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Peter Meerlo
Ruth M. Benca
Ted Abel *Editors*

Sleep, Neuronal Plasticity and Brain Function

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Sleep, Neuronal Plasticity and Brain Function

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Preface

Sleep is truly one of the biggest mysteries in behavioral neuroscience. Humans spend a substantial portion of their lives asleep, as do all other mammalian and bird species that have been studied to date, yet the functions of sleep remain elusive and continue to be a topic of debate among sleep researchers. This debate is complicated by the fact that there are two completely different forms of sleep, slow-wave sleep and rapid-eye-movement sleep, each of which may have its own function. Many of the modern hypotheses on the possible functions of sleep presume that it serves some crucial roles in neuronal recovery, maintenance, and plasticity, which ultimately are important for brain function in terms of alertness, information processing, memory formation, and emotional regulation. Indeed, while we are only beginning to understand how sleep supports brain function at the molecular and cellular level, sleep loss has an undeniable negative impact on behavioral performance and well-being. Moreover, accumulating evidence suggests that chronically restricted or disrupted sleep may contribute to age-related cognitive decline and psychiatric disorders such as schizophrenia and depression. This book reviews current knowledge on the importance of sleep for brain function, from molecular mechanisms to behavioral output, with special emphasis on the question of how sleep and sleep loss ultimately affect cognition and mood.

The opening chapters of this book describe sleep at the behavioral and electrophysiological level and define the different forms and stages of sleep. They also explain the principles of sleep homeostasis, which suggests that a need for sleep builds up as a consequence of the brain's activity during wakefulness.

One proposed homeostatic function of sleep is to globally downscale the strength of synapses that have been potentiated as a consequence of neuronal activity during waking. The core claim of this hypothesis is that experience and input during wakefulness are associated with a net increase in synaptic strength. In turn, sleep is thought to provide synaptic renormalization and this reset of synaptic strength would then enable processing of new information next day. However, sleep does not appear to have a single effect on synaptic strength. An unbiased review of the literature indicates that effects of sleep vary depending on, for example, the type of waking experience that precedes sleep and the type of neuronal

synapse under examination. In fact, another popular theory proposes that sleep is crucially involved in certain forms of Hebbian plasticity, which include input-specific strengthening of synapses that presumably underlie the formation of memory and long-term storage of information in the brain. Data in support of these different views on the role of sleep in synaptic plasticity are presented and discussed.

Several chapters in this book together provide an extensive overview of the latest insights into the role of sleep in regulating gene expression, synaptic plasticity, and neurogenesis, and how that in turn is linked to learning and memory processes. State-of-the-art techniques such as optogenetics and pharmacogenetics are being employed in rodent models to unravel the molecular and cellular mechanisms underlying sleep-related memory processes. Brain imaging methods in humans are used to characterize the functional neuroanatomy of sleep stages and to assess regional changes in brain activity during learning and subsequent memory processing during sleep. These imaging methods provide an important window on the brain that helps to bridge the gap between established and well-developed behavioral learning paradigms in humans and molecular measurements in model species such as rats, mice, birds, and flies. Together, these different methods and approaches applied in a variety of different mammalian and non-mammalian species have clearly established that sleep helps to transform newly learned information or skills into robust memories. In humans, even a properly timed nap may have positive effects on the formation of memories. Moreover, beyond helping to store information, sleep may also promote the flexible combination of information and thereby contribute to insightful behavior.

Obviously, the notion that sleep plays an important role in the regulation of neuronal plasticity and synaptic strength implies that insufficient sleep may have serious repercussions for brain function. Given the high incidence of restricted and disrupted sleep in our society this is an extremely pressing issue. Many people experience insufficient sleep on a regular basis due to our modern around-the-clock lifestyle, high work pressure, psychosocial stress, or sleep disorders. While acute sleep disruption can have a major and immediate impact on cognitive function and reduce the capacity to learn and form new memories in otherwise healthy subjects, chronic and progressive changes in sleep architecture and sleep quality may contribute to the cognitive decline that is seen with both normal aging and, to a much greater extent, neurodegenerative diseases.

Disturbed sleep may also explain symptoms of specific psychiatric disorders. One of the chapters discusses the dysfunction of sleep-mediated plasticity in schizophrenia patients and offers suggestions on how the study of sleeping brain activity can shed light on the pathophysiological mechanisms of this disorder. The relationship between sleep complaints and mental illness is particularly strong in the case of depression. Sleep complaints often precede the onset of depression and constitute an independent risk factor for the development of this mood disorder. Instead of being a symptom, insufficient sleep may act as a causal factor that sensitizes individuals, contributes to the development of depression, exacerbates the symptoms, and reduces the efficacy of pharmacological treatment. Because sleep is

considered to play a crucial role in regulating neuronal plasticity and synaptic strength, chronically insufficient sleep may contribute to psychiatric disorders through an impairment of these plasticity processes, leading to altered connectivity and communication within and between brain regions involved in the regulation of mood and cognitive function. Yet, a major unresolved issue in the field of sleep research is the paradox of sleep deprivation therapy discussed in one of the final chapters. While evidence is accumulating that chronically insufficient sleep may be a causal factor that increases the risk for depression, once people are depressed many of them respond positively to a night of sleep deprivation. Although this phenomenon seems contradictory, it clearly underscores the importance of sleep-related processes in the regulation and dysregulation of mood.

The closing chapter provides an extensive overview of the pharmacological treatment of sleep complaints and sleep disorders, particularly in relation to drug effects on neuronal plasticity processes. Various lines of evidence suggest that sleep disorders may negatively affect neuronal plasticity and cognitive function. Pharmacological treatments may alleviate these effects but may also have adverse side effects by themselves. Understanding the complex processes underlying neuroplasticity may lead to targeted pharmacotherapy and help in the design of drugs that can restore and enhance brain function in patients with sleep disorders.

All together, the chapters in this volume provide an extensive overview of the relationship between sleep, neuronal plasticity, and brain function and they illustrate the exciting developments and progress being made in the fields' attempts to unravel the mysteries of sleep. This book will be of interest to students, researchers, and clinicians with a general interest in brain function or a specific interest in sleep and sleep disorders.

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Contents

Behavioral and Electrophysiological Correlates of Sleep and Sleep Homeostasis

Tom Deboer

Abstract The definition of what sleep is depends on the method that is applied to record sleep. Behavioral and (electro)-physiological measures of sleep clearly overlap in mammals and birds, but it is often unclear how these two relate in other vertebrates and invertebrates. Homeostatic regulation of sleep, where the amount of sleep depends on the amount of previous waking, can be observed in physiology and behavior in all animals this was tested in. In mammals and birds, sleep is generally subdivided into two states, non-rapid eye movement (NREM) sleep and REM sleep. In mammals the combination of behavioral sleep and the changes in the slow-wave range of the NREM sleep electroencephalogram (EEG) can explain and predict the occurrence and depth of sleep in great detail. For REM sleep this is far less clear. Finally, the discovery that slow-waves in the NREM sleep EEG are influenced locally on the cortex depending on prior waking behavior is an interesting new development that asks for an adaptation of the concept of homeostatic regulation of sleep. Incorporating local sleep into models of sleep regulation is needed to obtain a comprehensive picture.

Keywords Sleep · Mammals · Birds · Behavior · Electroencephalography · Sleep homeostasis · Local sleep · Function of sleep

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Contents

1 What is Sleep?

1.1 Sleep is a Behavior: Rest and Activity

Before we can try to understand the basics of sleep and wakefulness, it should first be clear what is meant when the words 'wakefulness' and 'sleep' are used. In the most general description, wakefulness is a (daily recurring) state of the brain in which an individual organism engages in coherent cognitive and behavioral responses to the external world. These responses consist of (among others), locomotor activity, the ingestion of nutrients, reproduction, and communication. In most of these, sleep is the opposite of wakefulness. All we can see from the outside, when an animal is asleep, is that it is inactive. However, there are certain features of this inactive state that distinguish it from other inactive conditions. These include behavioral features proposed by Pieron (1913) with later additions made by Flanigan (1972) and Tobler (1984). During sleep, animals show a reduced reaction to stimuli, which distinguishes sleep from quiet wakefulness. However, this situation is easily reversed, which distinguishes sleep from other inactive states like hibernation, coma, or death. In addition, sleep as a behavior typically occurs at a species specific time of day, at a specific site and in a specific posture.

Based on these features, sleep-like behavior can be identified and investigated in many different species in the animal kingdom. Sleep as a resting state in invertebrates is investigated in great detail in bees and fruit flies, but also other insects and animals from other invertebrate phyla have been investigated (in the past reviewed by Campbell and Tobler 1984). Specific sleep postures and sleep sites have been described in the marine mollusk *Aplysia* (Strumwasser 1971), and in many insect species (Fiebrig 1912; Pittioni 1933; Rau 1938; Rau and Rau 1916; Sharplin 1963; Young 1935). The specific sleep postures were associated with an elevated arousal threshold in *Octopus vulgaris* (Lafont 1870), scorpions (Tobler and Stalder 1988), moths (Andersen 1968), and other insects (Blest 1958, 1960a, b).

Detailed research in bees showed that these animals show the complete spectrum of behavioral changes encompassing sleep, similar as in birds and mammals (Kaiser 1988; Sauer et al. 2004), but that they also show similar changes in physiology. These latter changes include a decrease in body temperature and muscle tone (Kaiser 1988) and changes in neuronal activity (Kaiser and Steinerkaiser 1983), showing that all these changes may be universal for sleep.

The last decades, the fruit fly (*Drosophila)* is by far the most intensely investigated invertebrate species in sleep research. Particularly, since the start of this century, the genetics of sleep has driven the development of different automated rest-activity recording methods for drosophila (ultrasound, camera tracking, or movement detection) to such heights that these variables in this species can now be monitored in great detail. It was shown, that drosophila not only shows a typical site and posture with increased arousal threshold during sleep-like behavior, but that it is modulated by stimulants and hypnotics, in a similar way as in mammals (Hendricks et al. 2000; Shaw et al. 2000).

Also in vertebrate species, automated rest-activity recordings are applied to determine sleep-like behavior. They are an important supporting tool in sleep research as they are non-invasive and relatively easy to use for a longer period of time with many subjects participating simultaneously. Actigraphy, with a wrist-worn monitor, is the standard procedure to observe rhythms in human subjects when entering a sleep experiment, or to perform a preliminary screen for sleep or circadian rhythm pathology in patients with sleep disorders (Ancoli-Israel et al. 2003). Actigraphy can also be used on children and infants, for instance to monitor the development of day–night rhythms (Jenni et al. 2006). Another application of actigraphy is the recording of long-term rest-activity rhythms in larger animals under natural conditions, for instance reindeer under polar light conditions (van Oort et al. 2005).

In genetically manipulated mice, rest-activity recordings have also become an important tool as a preliminary screen for changes in sleep and circadian rhythms. Rodents cannot carry an actigraph, and therefore, their rest-activity behavior is usually monitored by automated recording of running wheel activity rotations. As these recordings are influenced by several environmental cues [i.e., availability and size of the wheel, availability and quality of light (Banjanin and Mrosovsky 2000; Deboer and Tobler 2000a; Kas and Edgar 1999; Mrosovsky et al. 1998)], it is important to perform wheel-running experiments under well-defined environmental conditions. For instance, it has been shown that the availability of a running wheel influences the occurrence and distribution of sleep (Vyazovskiy et al. 2006). Another method to record activity patterns is by using passive infrared (PIR) detectors. The PIR detector is adapted from the infrared sensors normally placed above automatic sliding doors. It is placed above the cage and detects movement of the animals due to changes in the distribution of heat radiation in the cage. It can therefore only detect movement of euthermic animals. Recently video recording setups, which automatically score sleep-wake behavior, have been developed. Under well-defined circumstances, a high correlation with electroencephalogram (EEG) confirmed sleep can be achieved (Fisher et al. 2012; McShane et al. 2012).

With some additional quantification even REM sleep may be assessed (McShane et al. 2012), although the success rate of the latter is lower and needs further confirmation.

All of these methods are advantageous for high-throughput screening, but not for a detailed analysis of sleep. For vertebrates, particularly mammals and birds, there is another method to determine vigilance states, which depends on recording the electrical activity in the cortex (electroencephalography) together with other physiological variables (muscle activity, eye movements), and defines sleep states as different physiological states of the brain (see *Sleep is a brain state*). There seems to be a close correlation between the recorded rest-activity profile obtained from PIR or video, and the occurrence of electroencephalographic confirmed sleep and wakefulness (Farajnia et al. 2012; Fisher et al. 2012; McShane et al. 2012). However, there is not always a strong correlation between running wheel activity and sleep (Antle et al. 2012).

The intensity or depth of sleep can vary over time (see *Sleep is a brain state*). Until now, behavioral observations cannot provide a measure for the intensity or depth of the recorded rest or sleep [but see the cockroach for a possible exception (Tobler and Neuner-Jehle 1992)]. Only by determining the arousal threshold, and by that disturbing the animal, it is possible to get a measure for the depth of sleep. By comparing arousal thresholds with the EEG patterns, it is possible in mammals to overcome some of these limitations.

1.2 Sleep is a Brain State: The Electroencephalogram

The discovery of electrical activity of the brain in the 1870s (Caton 1875, 1877) was an important breakthrough in brain research. It laid the foundation for the development of the EEG by Hanns Berger (1929) and eventually modern polysomnography (PSG).

The EEG is a record of the fluctuations of electrical activity of the brain, which is recorded from the surface of the scalp. It is used to distinguish sleep states but also for diagnostics of cerebral dysfunctions. To record the EEG, a minimum of two electrodes are necessary. The active electrode is placed above the area of interest and an indifferent electrode is placed at a distance. The majority of the recorded signals originate from extracellular current flow, associated with the summed post-synaptic activity in synchronously activated vertically oriented pyramidal cells. When recording human sleep, both in research and in the clinic, many electrodes are placed on well-described areas of the head according to a conventional scheme (Keenan and Hirshkowitz 2011). The major frequencies recorded from the scalp during a normal sleep recording vary between 0.1 and 50 Hz and the amplitudes typically range between 20 and 300 μV. The frequency and amplitude characteristics of the EEG are rather complex, and may vary in the course of a recording session. However, a few dominant frequencies can be observed in the human EEG (Fig. 1). They are named after letters of the Greek

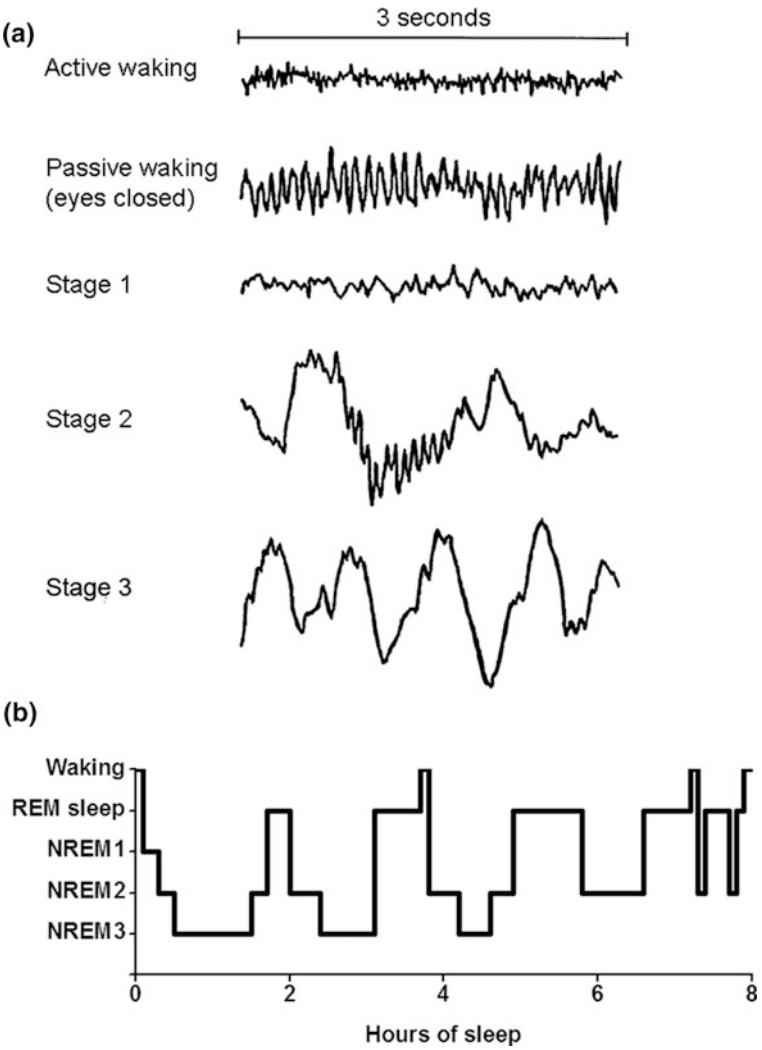

Fig. 1 **a** Detailed 3 s electroencephalographic records with specific features visible during certain sleep stages in humans with (from *top* to *bottom*), Beta-activity during active waking, alpha activity during waking with eyes closed, theta activity during NREM sleep stage 1, K-complex and spindle activity (12–15 Hz) during stage 2, and delta activity during stage 3. **b** Schematic hypnogram of a normal human night sleep, with waking, the three NREM sleep states and REM sleep. Note the predominance of deep NREM sleep (NREM3) with high amplitude slow-waves at the beginning of the night and the long REM sleep episodes at the end of the night

alphabet. Alpha waves (8–13 Hz) are mainly visible during relaxed waking with eyes closed. These are the first EEG waves distinguished by Hanns Berger (1929). Beta waves (13–30 Hz) are mainly visible during normal waking. Delta waves

(0.5–4.0 Hz) are visible during deep non-rapid eye movement (NREM) sleep, whereas theta waves (4–7 Hz) are visible during the first stage of NREM sleep. During the initial stages of sleep, at the transition to deep NREM sleep in humans, also K-complexes (a sharp single slow-wave) and spindles (a short burst of 12–15 Hz) can be observed.

Modern day PSG in humans combines the recording of the EEG with recording of muscle activity (electromyography, EMG), eye movements (electrooculography, EOG), heart rate (electrocardiogram, ECG), and respiration, but the EEG remains the backbone of sleep research in humans. Since the end of the 1960s, sleep staging in humans was mainly done according to the definitions of Rechtschaffen and Kales (1968) with one waking state, four NREM sleep states, and REM sleep. In 2007, the American Academy of Sleep Medicine (AASM) published a manual with new recommendations for recording methods and terminology (Iber et al. 2007). In this manual, the deep states of NREM sleep (states 3 and 4) are lumped together in one NREM sleep state (state 3 or slow-wave sleep; SWS). In addition, the manual contains rules for arousal, cardiac, movement, and respiratory events which add value to the clinical assessment of sleep disturbances and sleep-related illnesses. However, the specifications given by the AASM for recording and scoring of normal healthy sleep are not without controversy (Danker-Hopfe et al. 2009; Miano et al. 2010; Moser et al. 2009; Novelli et al. 2010). With these specifications for sleep state scoring it is possible to provide a record of the sleep-wake architecture over an entire night (Fig. 1b).

In other mammals and birds, in general, three states (waking, NREM sleep, and REM sleep) are distinguished. In Fig. 2, examples are given for EEG and EMG recordings in a mouse for the three vigilance states. With the electrode placement in mice, as described previously (Deboer et al. 2007b, 2013; Huber et al. 2000a), the EEG predominantly shows theta activity ($\sim$ 7 Hz) during waking and REM sleep, whereas in NREM sleep, high amplitude slow-waves ($<$ 5 Hz) predominate. During sleep EMG levels are low, whereas during waking EMG activity is higher. In some animal studies, NREM sleep is divided into deep NREM sleep, with high amplitude slow-waves and light NREM sleep with a lower EEG amplitude. In studies interested in REM sleep regulation or REM sleep-related phenomena, an intermediate or transitional state between NREM and REM sleep may be identified (Deboer et al. 1998; Gottesmann 1996). Although the vigilance states waking, NREM sleep, and REM sleep show large similarities in their behavior between mammalian species, the EEG and its spectral composition (Fig. 2, right panels) may differ (compare for instance human EEG (Borbely et al. 1981) with rat EEG (Borbely et al. 1984)). The latter may be due to differences between species in brain anatomy, but also because electrodes may not always be positioned at similar anatomical sites of the different species.

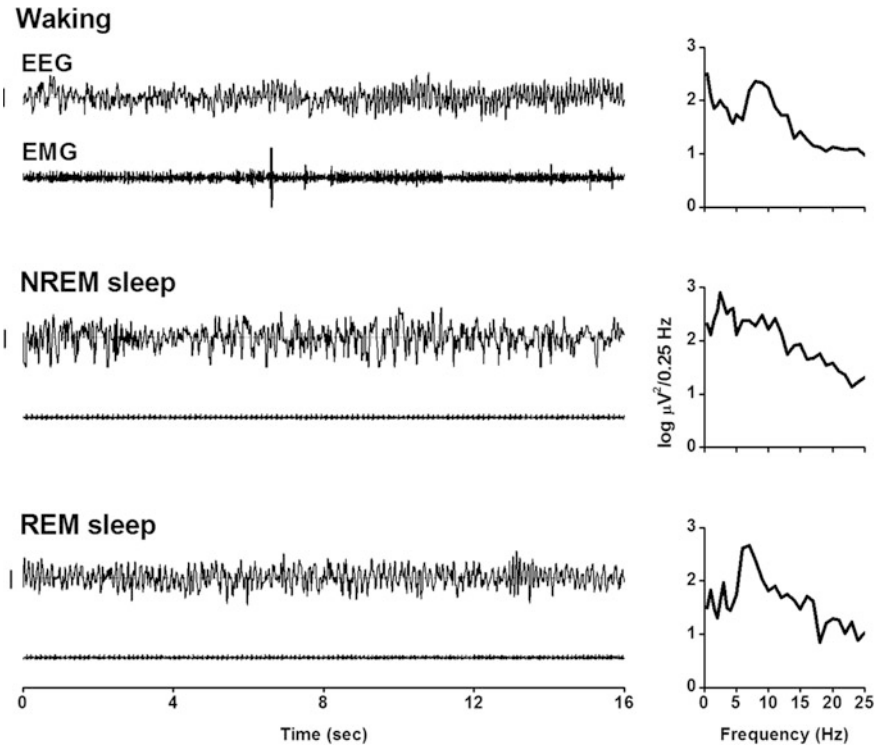

Fig. 2 *Left panels*Detailed electroencephalogram (EEG) and electromyogram (EMG) traces of 16 s of a mouse. Classification of the vigilance states is based on the visual inspection of both signals. Note the low activity, with heart rate, in the EMG in both sleep states. During waking, EMG activity is high and the EEG shows high theta (∼7 Hz) activity. *Right panels* Spectral analysis of the corresponding EEG traces in the *left panel* by a fast Fourier Transform routine. Spectral analysis is a mathematical approach to quantify the composition of complex waveforms with the purpose to decompose the complex signal into its single frequency components. Applied to the EEG it provides the opportunity to not just recognize the different vigilance states and the corresponding dominant frequencies in the EEG (*left panels*, and Fig. 1) but the whole spectral composition of the EEG (*right panels*). Indicated is the average power density spectrum of the four 4-s epochs in the *left panel* in 30 frequency bins between 0.25 and 25 Hz plotted on a logarithmic scale. The slow-waves during NREM sleep are reflected by high activity in the delta band (below 4 Hz). REM sleep and waking are characterized by dominant activity in the theta band (5.25–7.0 Hz)

2 Sleep Homeostasis

2.1 Homeostasis of Sleep Behavior

As mentioned previously, sleep as a behavior can be distinguished from other similar states like coma, hibernation, and death through different sleep specific features. In addition, some kind of regulatory capacity to sleep can be observed.

When sleep is lost, this loss is, at least partly, compensated by extending and/or deepening subsequent sleep. This homeostatic aspect is thought to be one of the main regulatory processes in sleep and seems to be universal, as it is found in many different phyla of the animal kingdom. For instance, in many invertebrate species, like cockroaches, drosophila, bees, and scorpions an increase in rest was observed after rest deprivation, suggesting compensation after sleep loss (Hendricks et al. 2000; Sauer et al. 2004; Shaw et al. 2000; Tobler and Neuner-Jehle 1992; Tobler and Stalder 1988). In birds similar observation of increased sleep after sleep loss was done (Bobbo et al. 2008; Boerema et al. 2003; Tobler and Borbely 1988). Figure 3 illustrates this homeostatic response in a mammal. It shows the average hourly values of NREM sleep and REM sleep in a group of rats during a baseline day, and during and after they are subjected to a 6 h sleep deprivation. In the hours following the sleep deprivation, both NREM sleep and REM sleep values are enhanced above corresponding baseline levels. Similar data are obtained in different sleep laboratories with several different sleep deprivation and recording methods in different species, vertebrate, and invertebrate [for some other examples see (Deboer et al. 1994; Franken et al. 1991a; Hasan et al. 2012; Huber et al. 2000a, b; Shaw 2003)]. In monophasic sleeping species, like humans, the amount of sleep per hour is usually not much increased after sleep deprivation, but sleep is significantly extended. Despite this difference, all species show the same phenomenon of increased sleep. Another similarity between species is that the recovery of the amount of sleep is not complete. In the example in Fig. 3, the panels on the right show the amount of NREM sleep and REM sleep lost and regained during the 6-h sleep deprivation and subsequent 18-h recovery. Due to the sleep deprivation, the animals lose, on average, almost 200 min of NREM sleep and 50 min of REM sleep, but they do not regain this loss in the subsequent recovery. In the course of the dark period, the animals still lack 100 min of NREM sleep and 10–15 min of REM sleep, which is not recovered. If there is a sleep homeostatic response it does not involve complete homeostasis of the amount of sleep. Either it is incomplete homeostasis or there must be other ways of recovery instead.

2.2 Homeostasis in the NREM Sleep EEG

From almost the earliest days of EEG sleep research it was clear that a positive correlation exists between depth of sleep, measured by the duration and intensity needed for a sound to wake the subject or animal, and the prominence of slow-waves (< 5 Hz) in the NREM sleep EEG (Blake and Gerard 1937; Ferrara et al. 1999; Neckelmann and Ursin 1993; Rosa and Bonnet 1985; Williams et al. 1964). By applying a fast Fourier transform (see Fig. 2) to the EEG, delta activity or slow-wave activity (SWA, EEG power density between ~ 1 and 4 Hz) can be calculated and quantified. In all mammals with a clear main sleep and wake period (either diurnal or nocturnal), slow-waves in the NREM sleep EEG are prominent at the beginning of the main sleep period and SWA gradually decreases as sleep progresses. Moreover,

despite a few exceptions where the sleep deprivation may have been too stressful (Tobler and Jaggi 1987), in most mammalian and some bird species investigated, SWA in NREM sleep increases after sleep deprivation (reviewed in Deboer 2007; Rattenborg et al. 2009). Both are illustrated in Fig. 3 in the left bottom panel. Mammals seem to compensate for sleep loss by two different strategies. The amount of NREM sleep is increased, but also SWA in NREM sleep is increased. It proofed to be worthwhile to calculate a combined measure of cumulated SWA over time by multiplying NREM sleep SWA with NREM sleep time. The result is cumulative slow-wave energy (SWE, Fig. 3 right bottom panel). Although debated over with long or complex sleep deprivation protocols (Kim et al. 2007; Leemburg et al. 2010), the data after short sleep deprivations show that SWE lost during sleep deprivation can be totally recovered within a couple of hours. Finally, in humans it was shown that a nap of sufficient duration during the day decreases subsequent SWA in NREM sleep during the following night (Werth et al. 1996b).

In some mammalian species, a dose response relationship between waking duration and subsequent SWA in NREM sleep was established. An overview of these studies is shown in Fig. 4. Most species show an increase in SWA which depends on the prior sleep deprivation duration. However, there is a species specific difference in the speed of increase. Of the seven documented species, the Djungarian hamster is the animal with the fastest increase, whereas the tree shrew is the slowest and does not seem to show an increase with increasing time awake. The increase rates of the Wistar rat and European ground squirrel are similar to each other and also the increase rate of the cat and mouse are similar. Although not all data and species seem to be in a line with this idea, it has been suggested that there is a relation between the waking induced increase rate of SWA in NREM sleep and body or brain size of these species (Deboer et al. 1994). The odd ones out are the C57BL/6 mouse and the tree shrew. The latter indicates that other factors also play a role, but attempts to correlate sleep time over different species with various other parameters did not support any sleep physiological theory (Siegel 2005, 2009). Comparison between mouse strains suggests a genetic component for the build-up rate of sleep pressure (Franken et al. 2001; Huber et al. 2000a). More data, including more species, are needed to obtain a clearer picture.

Most of these results indicate that there is some kind of process which keeps track of the prior duration of sleep and waking. The level of this process is reflected in SWA of the NREM sleep EEG, and the changes in SWA are predictable. This invites the application of mathematical modeling and simulations of the homeostatic sleep response. Until now, they have been applied successfully in human (Achermann et al. 1993), rat (Franken et al. 1991b) and mouse (Franken et al. 2001; Huber et al. 2000a). Yet, although major progress has been made in our knowledge of how the slow-waves in the NREM sleep EEG are produced by the brain (Amzica and Steriade 1998; Timofeev et al. 2012), still little is known about how and why they are homeostatically regulated. It is generally accepted that the slow-waves somehow reflect sleep need and therefore provide a window on the function of sleep. However, what this function is, and whether there is a central sleep homeostat in the brain, remains a topic of research and debate.

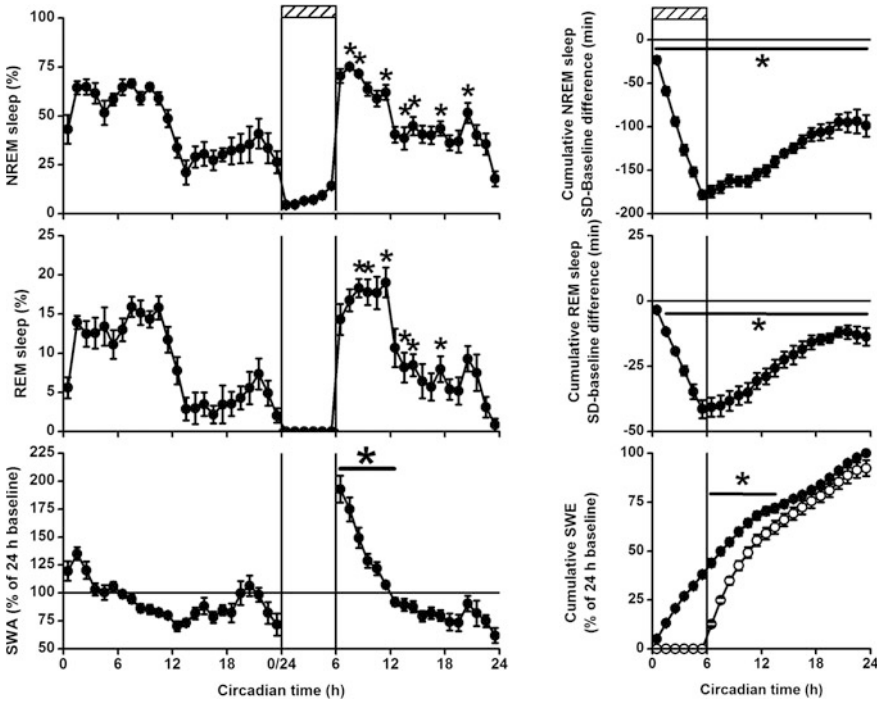

Fig. 3 *Left panels* Time course of 48 h of non-rapid eye movement (NREM) sleep, REM sleep, and slow-wave activity (SWA; EEG power density between 1 and 4 Hz) in NREM sleep across a baseline day, during a sleep deprivation performed during the first 6 h of the rest period (hatched bar at the *top*), and 18-h recovery in 1-h mean values (± SEM, $n = 11$). The recordings were obtained after 7 days adaptation to constant darkness. The vigilance states are expressed as a percentage of total recording time (= 100 %). SWA is expressed as the average over 24-h baseline (= 100 %). *Asterisks* and *solid lines* indicate where recovery significantly differed from baseline ($p < 0.05$, two-tailed paired *t*-test after significant ANOVA factor *day*). *Right top and middle panel* Cumulative NREM and REM sleep lost or gained. Plots are calculated by subtracting the minutes of sleep during deprivation (hatched bar at the *top*) and recovery from the corresponding baseline value and summing the difference with the preceding hour. Note that a significant part of the NREM sleep and REM sleep lost is not recovered. *Asterisks* and *solid lines* indicate where the sleep deprivation and recovery significantly differ from baseline ($p < 0.05$, two-tailed paired *t*-test after significant ANOVA). *Right bottom panel* Cumulative slow-wave energy (SWA*NREM sleep) for baseline (*dots*) and sleep deprivation/recovery (*circles*). Plots are calculated by summing the SWE with the previous hour. SWE is expressed as the total SWE over the 24-h baseline day (= 100 %). Note that SWE lost during the sleep deprivation is virtually totally recovered in the course of the recovery period. *Asterisks* and *solid lines* indicate where the recovery significantly differs from baseline ($p < 0.05$, two-tailed paired t-test after significant ANOVA factor *day*)

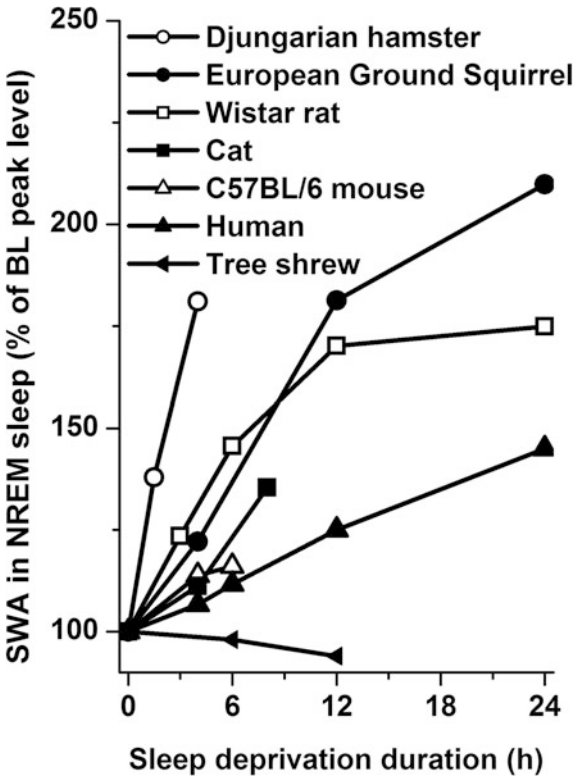

Fig. 4 Slow-wave activity (SWA; EEG power density between 1 and 4 Hz) in NREM sleep as a function of prior sleep deprivation duration in seven mammalian species. Animals were sleep deprived from the start of their main rest period when baseline SWA reaches its highest point. Data are plotted relative to this maximum baseline value. Note the difference in increase rate between the different species. Data of Djungarian hamster adapted from Deboer and Tobler (2003), C57BL/6 mouse from Huber et al. (2000a), Wistar rat from Tobler and Borbely (1986), European Ground Squirrel from Strijkstra and Daan (1998), Human from Akerstedt and Gillberg (1986), Cat from Lancel et al. (1991), and tree shrew from Coolen et al. (2012). Note the slower increase in SWA as brain and/or body size increases with the exception of the C57BL/6 mouse and the tree shrew

2.3 Changes in NREM Sleep Slow-Waves Independent of Waking Duration

Although, there is a clear relationship between waking duration and SWA in subsequent NREM sleep, several observations indicate that the occurrence of slow-waves in the NREM sleep EEG can change independent of waking duration. For instance, in infants, SWA in NREM sleep follows an alternating pattern, with high SWA in every second NREM sleep episode, independent of prior waking (Jenni et al. 2004). Also well documented is that the amplitude of slow-waves, and

therefore SWA decreases in the course of puberty (Campbell et al. 2012; Kurth et al. 2010). In the elderly, the amplitude of slow-waves further decreases (Dijk et al. 1989, 1999; Landolt et al. 1996). These changes in the expression of slow-waves in the course of puberty and adult aging all occur without affecting sleep homeostatic responsiveness.

Also the quality of sleep and waking may be influencing SWA. Disturbed sleep reduces the ability to produce high amplitude slow-waves in the NREM sleep EEG (Deboer et al. 2003; Dijk and Beersma 1989; Endo et al. 1997, 1998). In albino rats, light during the main sleep/rest period suppresses SWA in NREM sleep (Tobler et al. 1994). However, in pigmented mice such an influence was not observed (Deboer et al. 2007b), suggesting that pigmentation or light sensitivity may be the determining factor in this influence of light on slow-waves. That the quality of waking may influence subsequent slow-waves was shown by, for example, Meerlo et al. (1997). Rats that were exposed to a brief period of intense social stress, i.e., had an encounter with an aggressive dominant conspecific, showed an increase in SWA during subsequent NREM sleep. This increase was larger than the level normally obtained after non-stressful sleep deprivation of similar duration. The authors speculated that the stressful social encounter may have represented a period of intense wakefulness causing a more rapid build-up of sleep debt.

Even the time of day where the spontaneous or induced waking occurs, seems to influence the subsequent SWA response in the NREM sleep EEG (Deboer 2009; Vyazovskiy et al. 2007; Werth et al. 1996b). This suggests an influence of the endogenous circadian clock on the expression of slow-waves, either indirectly by modulating the quality of waking in a circadian pattern, or directly by influencing the expression of slow-waves in the EEG.

Pharmacological manipulations can also influence the expression of slow-waves. Caffeine is well known to increase alertness during the day. In addition, it was shown in humans and animals that it also delays sleep onset and reduces SWA during subsequent NREM sleep (Deboer et al. 2013; Landolt et al. 1995a, b; Schwierin et al. 1996). Caffeine is thought to influence sleep propensity by blocking the adenosine receptors. In accordance with that, stimulating the adenosine A1 receptor increases sleep and SWA in NREM sleep (Benington et al. 1995; Deboer et al. 2013; Schwierin et al. 1996).

There are several other pharmacological manipulations that also influence sleep and SWA. Atropine induces high amplitude slow-waves without affecting sleep (Bringmann 1995; Schaul et al. 1978). Benzodiazepines increase NREM sleep, but reduce slow-waves (Bastien et al. 2003). Other substances enhance NREM sleep duration and SWA simultaneously, like tumor necrosis factor, growth hormone releasing hormone, and interleukin-1 (Obal and Krueger 2003). Others decrease SWA, but still increase the amount of NREM sleep, like nerve growth factor, neurotropin-4, and obestatin (Szentirmai and Krueger 2006). Not all pharmacological agents which influence the occurrence of sleep or SWA in the NREM sleep EEG are related to normal physiological changes in sleep or sleep pressure. For instance, gamma-hydroxybutyrate does not show a sleep promoting effect but at

higher doses of GHB, EEG hyper synchronization with increased SWA together with a coma-like state is observed (Meerlo et al. 2004). Therefore, always the question should be asked whether the sleep-like state seen is true physiological sleep.

The genetic makeup can also influence the occurrence and strength of SWA in NREM sleep. In humans, an influence on SWA in NREM sleep was found in polymorphisms of genes influencing the level of adenosine in intracellular space (Bachmann et al. 2012; Retey et al. 2005), and polymorphisms in the per3 gene (Viola et al. 2007). In rodents, it was already shown in the 1970s that inbred mouse strains show differences in the occurrence and amplitude of slow-waves in the NREM sleep EEG (Valatx et al. 1972). Later it was shown that mouse strains show distinct differences in their EEG power density spectra (Franken et al. 1999; Huber et al. 2000a), and some of these differences were linked to differences in the genetics between the strains (Tafti and Franken 2002).

Finally, natural hypothermic states, like daily torpor and hibernation, can also change the occurrence of slow-waves during subsequent NREM sleep. Both after daily torpor and hibernation, animals show an increase in NREM sleep and SWA (Daan et al. 1991; Deboer and Tobler 1994; Trachsel et al. 1991). Combining daily torpor with sleep deprivations, it was shown in Djungarian hamsters that the increase in SWA after torpor was genuinely sleep-wake dependent. The animals postponed their deep NREM sleep with high SWA to a later time, when a sleep deprivation was applied (Deboer and Tobler 2000b). However, in ground squirrels, a sleep deprivation after hibernation made the subsequent increase in SWA disappear, indicating that it did not reflect the usual sleep-wake dependency (Larkin and Heller 1998; Strijkstra and Daan 1998). Research into this area has come more or less to a standstill and the discrepancy between hibernation and daily torpor has not been resolved until now (reviewed in Deboer 2005). Recently, it was shown that inducing a torpid like state in rats results in increased NREM sleep and SWA after rewarming (Cerri et al. 2013), similar to the findings obtained after daily torpor or in the course of hibernation.

The list of possible influences on SWA in NREM sleep, other than the duration of prior sleep and waking duration, shows that slow-waves may not only be an expression of a sleep homeostatic process, but may depend on global or local brain circuitry which can be manipulated by pharmacological agents and behavioral changes.

2.4 Local NREM Sleep Homeostasis

The observation that the dolphin exhibits deep slow-wave sleep only in on hemisphere simultaneously (Mukhametov et al. 1977), triggered the idea that sleep homeostasis may also have a local cortical component. Interestingly, experiments with selective deprivation of unihemispheric sleep in dolphins resulted in a unihemispheric slow-wave sleep rebound (Oleksenko et al. 1992). The data showed

that sleep, and therefore the sleep homeostatic process, is not necessarily a global process, running in parallel in the entire brain. More recently, in land living mammals, it was shown that the time constants of the decrease rate of SWA and therefore the hypothetical homeostatic recovery process differs between cortical areas of the brain (Huber et al. 2000b; Palchykova et al. 2002; Rusterholz and Achermann 2011; Werth et al. 1996a, 1997). These findings supported the notion that a use-dependent local cortical mechanism may underlie the sleep deprivation induced changes in the slow-waves of the NREM sleep EEG (Benington and Heller 1995; Krueger et al. 1999).

This idea was tested in many different ways in many different mammalian species. Pioneering work by the group of Alex Borbely showed that local activation of a particular cortical area during waking results in EEG changes recorded from the same cortical area during subsequent sleep (Kattler et al. 1994). A vibratory stimulus was applied to the hand to activate the contralateral somatosensory cortex. The effect on the subsequent sleep EEG was most prominent in the slow-wave range of the EEG, and was restricted to the derivation, corresponding with the same cortical area. Subsequent research stimulating the barrel cortex via the vibrissae in mice (Vyazovskiy et al. 2004), the motor cortex with running wheel activity in mice (Vyazovskiy et al. 2006), or the use of paw preference in rats (Vyazovskiy and Tobler 2008), showed that this is probably a universal property in mammals. An elegant experiment in humans applying a motor learning task (Huber et al. 2004a), which involves a restricted part of the cortex, confirmed the notion that local cortical SWA during NREM sleep can be changed under influence of the workload during previous waking in that particular part of the cortex. Recent data in the rat show that animals that are awake, which is confirmed by the global EEG, on a local cortical level can express slow-waves of which the timing correlates with hits and misses on a reaching task (Vyazovskiy et al. 2011). Together the data indicate that the occurrence of slow-waves and their homeostatic changes can be a local cortical phenomenon.

The discovery of this local cortical homeostasis in slow-waves may have consequences for our thinking about sleep homeostasis and its relation with sleep regulatory mechanisms. Local sleep homeostasis shows that the occurrence of slow-waves, which was previously thought to be a marker for a global sleep homeostat, is influenced by use-dependent local processes. The fact that sleep regulatory models, based on SWA, have some predictive value, concerning the timing of sleep, suggests that these local changes in sleep homeostasis may be translated into a general signal influencing the switch between sleep and wakefulness. This may require that one or more brain regions involved in sleep regulation monitors local sleep homeostasis over the entire cortex. Candidate areas are those involved in sleep regulation on the neuronal level. These include histaminergic tuberomammilary nucleus (TMN) of the hypothalamus, noradrenergic cells in the locus coeruleus (LC), serotonergic cells from the dorsal raphe (DR) nucleus, and cholinergic cells in the pons (Saper et al. 2001). Next to inhibiting sleep promoting neurons in the ventrolateral preoptic area, the aminergic neurons from TMN, LC, and DR are thought to promote waking via excitation of arousal

systems in the hypothalamus, thalamus, basal forebrain (BF), and cortex. Inhibition of cholinergic neurons in the BF by release of adenosine promotes NREM sleep (Jones 2004). Alternation between NREM and REM sleep is thought to be caused by cholinergic, serotonergic, and norepinephrinergic systems in the pons, LC and DR (McCarley and Massaquoi 1992). In addition, the endogenous clock, residing in the suprachiasmatic nucleus of the hypothalamus (Meijer and Rietveld 1989) is thought to provide the sleep–wake neuronal mechanisms with a circadian framework, promoting sleep and waking at the proper time of the day.

That changes in cortical activity may influence these deeper brain areas are not as unlikely as it may seem. In the past, we have observed a correlation between the activity of neurons in the suprachiasmatic nucleus and SWA in NREM sleep (Deboer et al. 2003, 2007a). This finding shows that changes related to sleep homeostasis can also be found in the activity of neurons in deeper brain areas. For the sleep homeostatic model to work, it may require a general field detector of local cortical sleep homeostasis to be located in a brain area involved in sleep initiation and maintenance.

Whether we look at sleep as a behavior or as a physiological brain state, the homeostatic component is visible in both behavior and physiology and can be seen as a general and defining property of sleep in all animals. In mammalian and bird sleep, the analysis of changes in the sleep, EEG in relation to sleep–wake duration has become very important. The discovery of local cortical sleep-like phenomena sheds new light on sleep physiology and implementing these into models of sleep regulation is needed for a comprehensive picture of the mechanisms of sleep regulation.

2.5 REM Sleep Homeostasis, or Not?

NREM and REM sleep alternate in a cyclic pattern and the occurrence of REM sleep can be described in cyclic interaction models (McCarley and Massaquoi 1992), which results in a fairly constant ratio between NREM and REM sleep under undisturbed baseline conditions. Next to that, in humans, REM sleep is strongly influenced by the circadian clock (Carskadon and Dement 1975; Dijk and Czeisler 1995; Lavie and Scherson 1981), but in rodents this may be less the case (Yasenkov and Deboer 2010, 2012).

REM sleep often displays a rebound increase after sleep deprivation (Fig. 3; Borbely and Neuhaus 1979; Borbely et al. 1984; Dement 1960) and it is still generally believed that REM sleep recovery largely occurs through an increase in REM sleep time. However, similar to NREM sleep this recovery is generally not complete (Fig. 3). A number of studies have reported subtle changes in the REM sleep EEG following sleep deprivation, particularly in the theta frequency range, suggesting that REM sleep quality or intensity may change as well (Borbely et al. 1984; Endo et al. 1998; Tobler and Borbely 1986). However, in contrast to the well-established homeostatic regulation of NREM sleep in relation to prior

wakefulness, rebounds in REM sleep time are less predictable and may only occur after longer sleep deprivation duration. In addition, it is still debated whether REM sleep is homeostatically regulated in relation to prior waking or to prior NREM sleep (Benington and Heller 1994; Franken 2002b; Ocampo-Garces et al. 2000). The analysis of REM sleep regulation is complicated by the fact that the expression of REM sleep is also highly sensitive to modulation by various other factors. For example, brain temperature (Deboer and Tobler 1996; Parmeggiani et al. 1975), environmental temperature (Amici et al. 1998, 2008; Roussel et al. 1984), and stress (Meerlo et al. 2001; Rampin et al. 1991; Sanford et al. 2010) are shown to influence the occurrence of REM sleep. Moreover, the influence of stress is not unambiguous. Uncontrollable foot-shock stress significantly suppresses REM sleep, but with no subsequent rebound (Sanford et al. 2010). In contrast, exposure to immobilization stress, with only minor loss of REM sleep, increases subsequent REM sleep beyond baseline levels (Meerlo et al. 2001; Rampin et al. 1991).

There is still no consensus on how REM sleep is regulated and by what (Benington 2002; Franken 2002a), and this may not be resolved until we know more about the function of REM sleep or when we discover the physiological substrate of REM sleep pressure.

3 Functional Implications

Life as we know it evolved on a rotating planet. As a result, almost all species developed a timing system that shows persistent circadian oscillations, even under constant conditions. Organisms that are able to predict daily changes in temperature, radiation and food availability have an advantage over organisms that cannot predict these changes (Ouyang et al. 1998; Woelfle et al. 2004). Depending on the environmental time, the organism is active or resting. In addition, the clock needs to coordinate and streamline internal physiology to optimize energy expenditure and the use of internal recourses. During the active phase ingestion and reproduction are prominent, during rest maintenance and growth. As soon as animals developed a central nervous system, this also became part of the already existing rest-activity cycle. One can hypothesize that for maintenance this organ needs to go off-line like the rest of the body, and this condition is what we now call sleep.

In contrast to activities like, foraging, eating, drinking, and mating, the benefits of sleep are unclear. However, the costs of sleep seem to be substantial. Sleep leaves the animal defenseless for more or less a third of its life, and if it were not essential, natural selection would long since have eliminated sleep. But until now, no vertebrate has been found which does not spend a significant amount of its life asleep (Campbell and Tobler 1984). That alone is already a strong indication that sleep is important. Disruption of sleep can have large consequences for health and well-being (Aldabal and Bahammam 2011; Baglioni et al. 2011; Durmer and Dinges 2005; Meerlo et al. 2008; Spiegel et al. 2009) and prolonged sleep

deprivation may lead to death (Everson et al. 1989; Kleitman 1927; Manaceine 1894). Sleep therefore seems to fulfill an important function, which cannot be fulfilled during wakefulness. In the history of its extensive scientific study, numerous theories for the function of sleep have been proposed and rejected and no satisfactory explanation for the necessity of sleep has been offered. The fact that in mammals and birds two distinct sleep states are found supports the notion that sleep may have at least two functions, and from an evolutionary perspective there may even be many functions of sleep.

Different biological disciplines came up with different explanation for the occurrence of sleep. Sleep was suggested to reduce predatory risks at certain times of the day (Meddis 1975) or to reduce body and brain temperature, preventing overheating (McGinty and Szymusiak 1990). Also theories related to energy balance were proposed. Either sleep was for energy conservation of the organism (Berger and Phillips 1995), or restocking energy reserves of the brain specifically, which was depleted during waking (Benington and Heller 1995). For REM sleep genetic reprogramming, strengthening psychological individuality (Jouvet 1998), but also removing undesirable modes of interactions in networks of cells of the cerebral cortex (Crick and Mitchison 1983), a certain type of regulated memory loss, was proposed. More recent theories suggest an important role for sleep in neuronal plasticity, or more specific, a role in learning and memory consolidation. For the latter, a large amount of data has been produced, but a lot remains unclear, also because there are several types of memory and at least two types of sleep (reviewed in Stickgold 2013). When it comes to neuronal plasticity there are a few theories with subtle differences available. It has been proposed that sleep stimulates the use and maintenance of synaptic connections which are not (or too little) used during waking (Krueger and Obal 1993). The opposite, e.g., sleep increases the sensitivity of synapses intensely used during waking has also been proposed (Kavanau 1997). A popular recent hypothesis proposes synaptic homeostasis, where during waking synaptic potentiation occurs, followed by sleep where, during NREM sleep, synaptic downscaling takes place (Tononi and Cirelli 2003, 2006). The synaptic homeostasis hypothesis is in accordance with sleep homeostatic mechanisms, and also the data showing local cortical homeostasis of SWA are in accordance with the synaptic homeostasis hypothesis. In addition, the hypothesis may also be able to explain why sleep is beneficial for learning and memory. On the other hand, not all available data are in agreement with the synaptic homeostasis hypothesis and, as with all previous theories on the function of sleep, it is heavily debated (Frank 2012).

Understanding sleep regulation and sleep function is crucial for understanding brain functioning. It can be concluded that this requires data and ideas from different methods, models, and research areas. Although great progress was made in the last century, many questions remain unanswered. Building on a multidisciplinary approach is important to increase our understanding in the decades to come.

References

Achermann P, Dijk DJ, Brunner DP, Borbely AA (1993) A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. Brain Res Bull 31:97–113

Akerstedt T, Gillberg M (1986) A dose-response study of sleep loss and spontaneous sleep termination. Psychophysiology 23:293–297

Aldabal L, Bahammam AS (2011) Metabolic, endocrine, and immune consequences of sleep deprivation. Open Respir Med J 5:31–43

Amici R, Zamboni G, Perez E, Jones CA, Parmeggiani PL (1998) The influence of a heavy thermal load on REM sleep in the rat. Brain Res 781:252–258

Amici R, Cerri M, Ocampo-Garces A, Baracchi F, Dentico D, Jones CA, Luppi M, Perez E, Parmeggiani PL, Zamboni G (2008) Cold exposure and sleep in the rat: REM sleep homeostasis and body size. Sleep 31:708–715

Amzica F, Steriade M (1998) Electrophysiological correlates of sleep delta waves. Electroencephalogr Clin Neurophysiol 107:69–83

Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP (2003) The role of actigraphy in the study of sleep and circadian rhythms. Sleep 26:342–392

Andersen FS (1968) Sleep in moths and its dependence on the frequency of stimulation in *Anagasta kuehniella*. Opusc Ent 33:15–24

Antle MC, van Diepen HC, Deboer T, Pedram P, Pereira RR, Meijer JH (2012) Methylphenidate modifies the motion of the circadian clock. Neuropsychopharmacology 37:2446–2455

Bachmann V, Klaus F, Bodenmann S, Schafer N, Brugger P, Huber S, Berger W, Landolt HP (2012) Functional ADA polymorphism increases sleep depth and reduces vigilant attention in humans. Cereb Cortex 22:962–970

Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, Lombardo C, Riemann D (2011) Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 135:10–19

Banjanin S, Mrosovsky N (2000) Preferences of mice, Mus musculus, for different types of running wheel. Lab Anim 34:313–318

Bastien CH, LeBlanc M, Carrier J, Morin CM (2003) Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. Sleep 26:313–317

Benington JH (2002) Debating how REM sleep is regulated (and by what). J Sleep Res 11:29–31

Benington JH, Heller HC (1994) Does the Function of Rem-Sleep Concern Non-Rem Sleep or Waking. Prog Neurobiol 44:433–449

Benington JH, Heller HC (1995) Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol 45:347–360

Benington JH, Kodali SK, Heller HC (1995) Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. Brain Res 692:79–85

Berger H (1929) Uber das Elektroenkephalogramm des Menschen. Arch Psychiatr Nervenkr 87:527–570

Berger RJ, Phillips NH (1995) Energy conservation and sleep. Behav Brain Res 69:65–73

Blake H, Gerard RW (1937) Brain potentials during sleep. Am J Physiol 119:692–703

Blest AD (1958) Some interactions between flight, protective display, and oviposition behaviour in *Callosamia* and *Rothschildia* spp. Behaviour 13:297–318

Blest AD (1960a) The evolution, ontogeny and quantitative control of the settling movements of some New World *saturniid* moths, with some comments on distiance communication by honeybees. Behaviour 16:188–253

Blest AD (1960b) The testing position of Cerodirphia seciosa (Cramer), (Lepidoptera, Saturniidae): the ritualization of a conflict posture. Zoologica 45:81–90

Bobbo D, Nelini C, Mascetti GG (2008) Binocular and monocular/unihemispheric sleep in the domestic chick (Gallus gallus) after a moderate sleep deprivation. Exp Brain Res 185:421–427

Boerema AS, Riedstra B, Strijkstra AM (2003) Decrease in monocular sleep after sleep deprivation in the domestic chicken. Behaviour 140:1415–1420

Borbely AA, Neuhaus HU (1979) Sleep-deprivation—effects on sleep and EEG in the rat. J Comp Physiol 133:71–87

Borbely AA, Baumann F, Brandeis D, Strauch I, Lehmann D (1981) Sleep deprivation: effect on sleep stages and EEG power density in man. Electroencephalogr Clin Neurophysiol 51:483–495

Borbely AA, Tobler I, Hanagasioglu M (1984) Effect of sleep deprivation on sleep and EEG power spectra in the rat. Behav Brain Res 14:171–182

Bringmann A (1995) Topographic mapping of the cortical EEG power in the unrestrained rat: peripheral effects of neuroactive drugs. Arch Ital Biol 133:1–16

Campbell SS, Tobler I (1984) Animal sleep: a review of sleep duration across phylogeny. Neurosci Biobehav Rev 8:269–300

Campbell IG, Grimm KJ, de Bie E, Feinberg I (2012) Sex, puberty, and the timing of sleep EEG measured adolescent brain maturation. Proc Natl Acad Sci U S A 109:5740–5743

Carskadon MA, Dement WC (1975) Sleep studies on a 90-minute day. Electroen Clin Neuro 39:145–155

Caton R (1875) The electric currents of the brain. Br Med J 2:278

Caton R (1877) Interim report on investigations of the electric currents of the brain. Br Med J Suppl L:62–65

Cerri M, Mastrotto M, Tupone D, Martelli D, Luppi M, Perez E, Zamboni G, Amici R (2013) The inhibition of neurons in the central nervous pathways for thermoregulatory cold defense induces a suspended animation state in the rat. J Neurosci 33:2984–2993

Coolen A, Hoffmann K, Barf RP, Fuchs E, Meerlo P (2012) Telemetric study of sleep architecture and sleep homeostasis in the day-active tree shrew Tupaia belangeri. Sleep 35:879–888

Crick F, Mitchison G (1983) The function of dream sleep. Nature 304:111–114

Daan S, Barnes BM, Strijkstra AM (1991) Warming up for sleep? Ground squirrels sleep during arousals from hibernation. Neurosci Lett 128:265–268

Danker-Hopfe H, Anderer P, Zeitlhofer J, Boeck M, Dorn H, Gruber G, Heller E, Loretz E, Moser D, Parapatics S, Saletu B, Schmidt A, Dorffner G (2009) Interrater reliability for sleep scoring according to the Rechtschaffen & Kales and the new AASM standard. J Sleep Res 18:74–84

Deboer T (2005) Cool hamsters get sleepy. J Therm Biol 30:173–178

Deboer T (2007) Technologies of sleep research. Cell Mol Life Sci 64:1227–1235

Deboer T (2009) Sleep and sleep homeostasis in constant darkness in the rat. J Sleep Res 18:357–364

Deboer T, Tobler I (1994) Sleep EEG after daily torpor in the Djungarian hamster: similarity to the effect of sleep deprivation. Neurosci Lett 166:35–38

Deboer T, Tobler I (1996) Shortening of the photoperiod affects sleep distribution, EEG and cortical temperature in the Djungarian hamster. J Comp Physiol A 179:483–492

Deboer T, Tobler I (2000a) Running wheel size influences circadian rhythm period and its phase shift in mice. J Comp Physiol A 186:969–973

Deboer T, Tobler I (2000b) Slow waves in the sleep electroencephalogram after daily torpor are homeostatically regulated. NeuroReport 11:881–885

Deboer T, Tobler I (2003) Sleep regulation in the Djungarian hamster: comparison of the dynamics leading to the slow-wave activity increase after sleep deprivation and daily torpor. Sleep 26:567–572

Deboer T, Franken P, Tobler I (1994) Sleep and cortical temperature in the Djungarian hamster under baseline conditions and after sleep deprivation. J Comp Physiol A 174:145–155

Deboer T, Sanford LD, Ross RJ, Morrison AR (1998) Effects of electrical stimulation in the amygdala on ponto-geniculo-occipital waves in rats. Brain Res 793:305–310

Deboer T, Vansteensel MJ, Detari L, Meijer JH (2003) Sleep states alter activity of suprachiasmatic nucleus neurons. Nat Neurosci 6:1086–1090

Deboer T, Detari L, Meijer JH (2007a) Long term effects of sleep deprivation on the mammalian circadian pacemaker. Sleep 30:257–262
Deboer T, Ruijgrok G, Meijer JH (2007b) Short light-dark cycles affect sleep in mice. Eur J Neurosci 26:3518–3523
Deboer T, van Diepen HC, Ferrari MD, Van den Maagdenberg AMJM, Meijer JH (2013) Reduced Sleep and Low Adenosinergic Sensitivity in Cacna1a R192Q Mutant Mice. Sleep 36:127–136
Dement W (1960) Effect of Dream Deprivation. Science 131:1705–1707
Dijk DJ, Beersma DG (1989) Effects of SWS deprivation on subsequent EEG power density and spontaneous sleep duration. Electroencephalogr Clin Neurophysiol 72:312–320
Dijk DJ, Czeisler CA (1995) Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15:3526–3538
Dijk DJ, Beersma DG, van den Hoofdakker RH (1989) All night spectral analysis of EEG sleep in young adult and middle-aged male subjects. Neurobiol Aging 10:677–682
Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA (1999) Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol 516(Pt 2):611–627
Durmer JS, Dinges DF (2005) Neurocognitive consequences of sleep deprivation. Semin Neurol 25:117–129
Endo T, Schwierin B, Borbely AA, Tobler I (1997) Selective and total sleep deprivation: effect on the sleep EEG in the rat. Psychiatry Res 66:97–110
Endo T, Roth C, Landolt HP, Werth E, Aeschbach D, Achermann P, Borbely AA (1998) Effect of frequent brief awakenings from nonREM sleep on the nonREM-REM sleep cycle. Psychiatry Clin Neurosci 52:129–130
Everson CA, Bergmann BM, Rechtschaffen A (1989) Sleep deprivation in the rat: III. Total sleep deprivation. Sleep 12:13–21
Farajnia S, Michel S, Deboer T, vanderLeest HT, Houben T, Rohling JH, Ramkisoensing A, Yasenkov R, Meijer JH (2012) Evidence for neuronal desynchrony in the aged suprachiasmatic nucleus clock. J Neurosci 32:5891–5899
Ferrara M, De Gennaro L, Casagrande M, Bertini M (1999) Auditory arousal thresholds after selective slow-wave sleep deprivation. Clin Neurophysiol 110:2148–2152
Fiebrig K (1912) Schlafende Insekten. Jenaische Zeit. Naturwissenschaften 48:315–364
Fisher SP, Godinho SI, Pothecary CA, Hankins MW, Foster RG, Peirson SN (2012) Rapid assessment of sleep-wake behavior in mice. J Biol Rhythms 27:48–58
Flanigan WF (1972) Behavioral states and electroencephalograms of reptiles. In: Chase MH (ed) The sleeping brain. Unviersity of California at Los Angeles, Los Angeles, pp 14–18
Frank MG (2012) Erasing synapses in sleep: is it time to be SHY? Neural Plast 2012:264378
Franken P (2002a) Debating how REM sleep is regulated (and by what)—response. J Sleep Res 11:31–33
Franken P (2002b) Long-term vs. short-term processes regulating REM sleep. J Sleep Res 11:17–28
Franken P, Dijk DJ, Tobler I, Borbely AA (1991a) Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. Am J Physiol 261:R198–R208
Franken P, Tobler I, Borbely AA (1991b) Sleep homeostasis in the rat: simulation of the time course of EEG slow-wave activity. Neurosci Lett 130:141–144
Franken P, Malafosse A, Tafti M (1999) Genetic determinants of sleep regulation in inbred mice. Sleep 22:155–169
Franken P, Chollet D, Tafti M (2001) The homeostatic regulation of sleep need is under genetic control. J Neurosci 21:2610–2621
Gottesmann C (1996) The transition from slow-wave sleep to paradoxical sleep: evolving facts and concepts of the neurophysiological processes underlying the intermediate stage of sleep. Neurosci Biobehav Rev 20:367–387

Hasan S, Dauvilliers Y, Mongrain V, Franken P, Tafti M (2012) Age-related changes in sleep in inbred mice are genotype dependent. Neurobiol Aging 33(195):e113–e126
Hendricks JC, Finn SM, Panckeri KA, Chavkin J, Williams JA, Sehgal A, Pack AI (2000) Rest in Drosophila is a sleep-like state. Neuron 25:129–138
Huber R, Deboer T, Tobler I (2000a) Effects of sleep deprivation on sleep and sleep EEG in three mouse strains: empirical data and simulations. Brain Res 857:8–19
Huber R, Deboer T, Tobler I (2000b) Topography of EEG dynamics after sleep deprivation in mice. J Neurophysiol 84:1888–1893
Huber R, Ghilardi MF, Massimini M, Tononi G (2004a) Local sleep and learning. Nature 430:78–81
Huber R, Hill SL, Holladay C, Biesiadecki M, Tononi G, Cirelli C (2004b) Sleep homeostasis in Drosophila melanogaster. Sleep 27:628–639
Iber C, Ancoli-Israel S, Quan SF (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. American Academy of Sleep Medicine, Westchester
Jenni OG, Borbely AA, Achermann P (2004) Development of the nocturnal sleep electroencephalogram in human infants. Am J Physiol Regul Integr Comp Physiol 286:R528–R538
Jenni OG, Deboer T, Achermann P (2006) Development of the 24-h rest-activity pattern in human infants. Infant Behav Dev 29:143–152
Jones BE (2004) Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. Prog Brain Res 145:157–169
Jouvet M (1998) Paradoxical sleep as a programming system. J Sleep Res 7(Suppl 1):1–5
Kaiser W (1988) Busy bees need rest, too—behavioral and electromyographical sleep signs in honeybees. J Comp Physiol A 163:565–584
Kaiser W, Steinerkaiser J (1983) Neuronal correlates of sleep, wakefulness and arousal in a diurnal insect. Nature 301:707–709
Kas MJ, Edgar DM (1999) A nonphotic stimulus inverts the diurnal-nocturnal phase preference in Octodon degus. J Neurosci 19:328–333
Kattler H, Dijk DJ, Borbely AA (1994) Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. J Sleep Res 3:159–164
Kavanau JL (1997) Memory, sleep and the evolution of mechanisms of synaptic efficacy maintenance. Neuroscience 79:7–44
Keenan S, Hirshkowitz M (2011) Monitoring and staging human sleep. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 5th edn. Elsevier Saunders, St. Louis
Kim Y, Laposky AD, Bergmann BM, Turek FW (2007) Repeated sleep restriction in rats leads to homeostatic and allostatic responses during recovery sleep. Proc Natl Acad Sci U S A 104:10697–10702
Kleitman N (1927) Studies on the physiology of sleep V: some experiments on puppies. Am J Physiol 84:386–395
Krueger JM, Obal F (1993) A neuronal group theory of sleep function. J Sleep Res 2:63–69
Krueger JM, Obal F Jr, Fang J (1999) Why we sleep: a theoretical view of sleep function. Sleep Med Rev 3:119–129
Kurth S, Jenni OG, Riedner BA, Tononi G, Carskadon MA, Huber R (2010) Characteristics of sleep slow waves in children and adolescents. Sleep 33:475–480
Lafont A (1870) Journal d'observation faites sur les animaux marins du Bassin d'Arcachon; pendant les années 1866, 1867, 1868
Lancel M, van Riezen H, Glatt A (1991) Effects of circadian phase and duration of sleep deprivation on sleep and EEG power spectra in the cat. Brain Res 548:206–214
Landolt HP, Dijk DJ, Gaus SE, Borbely AA (1995a) Caffeine reduces low-frequency delta activity in the human sleep EEG. Neuropsychopharmacology 12:229–238
Landolt HP, Werth E, Borbely AA, Dijk DJ (1995b) Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. Brain Res 675:67–74

Landolt HP, Dijk DJ, Achermann P, Borbely AA (1996) Effect of age on the sleep EEG: slow-wave activity and spindle frequency activity in young and middle-aged men. Brain Res 738:205–212

Larkin JE, Heller CH (1998) The disappearing slow wave activity of hibernators. Sleep Res Online 1:96–101

Lavie P, Scherson A (1981) Ultrashort sleep-waking schedule. 1. Evidence of ultradian rhythmicity in sleepability. Electroen Clin Neuro 52:163–174

Leemburg S, Vyazovskiy VV, Olcese U, Bassetti CL, Tononi G, Cirelli C (2010) Sleep homeostasis in the rat is preserved during chronic sleep restriction. Proc Natl Acad Sci U S A 107:15939–15944

Manaceine M (1894) Quelques observations experimentales sur l'influence de l'insomnie absolue. Arch Ital Biol 21:322–325

McCarley RW, Massaquoi SG (1992) Neurobiological structure of the revised limit cycle reciprocal interaction model of REM cycle control. J Sleep Res 1:132–137

McGinty D, Szymusiak R (1990) Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. Trends Neurosci 13:480–487

McShane BB, Galante RJ, Biber M, Jensen ST, Wyner AJ, Pack AI (2012) Assessing REM sleep in mice using video data. Sleep 35:433–442

Meddis R (1975) On the function of sleep. Anim Behav 23:676–691

Meerlo P, Pragt BJ, Daan S (1997) Social stress induces high intensity sleep in rats. Neurosci Lett 225:41–44

Meerlo P, Easton A, Bergmann BM, Turek FW (2001) Restraint increases prolactin and REM sleep in C57BL/6 J mice but not in BALB/cJ mice. Am J Physiol-Reg I 281:R846–R854

Meerlo P, Westerveld P, Turek FW, Koehl M (2004) Effects of gamma-hydroxybutyrate (GHB) on vigilance states and EEG in mice. Sleep 27:899–904

Meerlo P, Sgoifo A, Suchecki D (2008) Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev 12:197–210

Meijer JH, Rietveld WJ (1989) Neurophysiology of the suprachiasmatic circadian pacemaker in rodents. Physiol Rev 69:671–707

Miano S, Paolino MC, Castaldo R, Villa MP (2010) Visual scoring of sleep: a comparison between the Rechtschaffen and Kales criteria and the American Academy of Sleep Medicine criteria in a pediatric population with obstructive sleep apnea syndrome. Clin Neurophysiol 121:39–42

Moser D, Anderer P, Gruber G, Parapatics S, Loretz E, Boeck M, Kloesch G, Heller E, Schmidt A, Danker-Hopfe H, Saletu B, Zeitlhofer J, Dorffner G (2009) Sleep classification according to AASM and Rechtschaffen & Kales: effects on sleep scoring parameters. Sleep 32:139–149

Mrosovsky N, Salmon PA, Vrang N (1998) Revolutionary science: an improved running wheel for hamsters. Chronobiol Int 15:147–158

Mukhametov LM, Supin AY, Polyakova IG (1977) Interhemispheric asymmetry of the electroencephalographic sleep patterns in dolphins. Brain Res 134:581–584

Neckelmann D, Ursin R (1993) Sleep stages and EEG power spectrum in relation to acoustical stimulus arousal threshold in the rat. Sleep 16:467–477

Novelli L, Ferri R, Bruni O (2010) Sleep classification according to AASM and Rechtschaffen and Kales: effects on sleep scoring parameters of children and adolescents. J Sleep Res 19:238–247

Obal F Jr, Krueger JM (2003) Biochemical regulation of non-rapid-eye-movement sleep. Front Biosci 8:d520–d550

Ocampo-Garces A, Molina E, Rodriguez A, Vivaldi EA (2000) Homeostasis of REM sleep after total and selective sleep deprivation in the rat. J Neurophysiol 84:2699–2702

Oleksenko AI, Mukhametov LM, Polyakova IG, Supin AY, Kovalzon VM (1992) Unihemispheric sleep deprivation in bottlenose dolphins. J Sleep Res 1:40–44

Ouyang Y, Andersson CR, Kondo T, Golden SS, Johnson CH (1998) Resonating circadian clocks enhance fitness in cyanobacteria. Proc Natl Acad Sci U S A 95:8660–8664

Palchykova S, Deboer T, Tobler I (2002) Selective sleep deprivation after daily torpor in the Djungarian hamster. J Sleep Res 11:313–319
Parmeggiani PL, Agnati LF, Zamboni G, Cianci T (1975) Hypothalamic temperature during sleep cycle at different ambient-temperatures. Electroen Clin Neuro 38:589–596
Pieron H (1913) Le Probleme Physiologique du Sommeil. Masson, Paris
Pittioni B (1933) Ueber Schlafgesellschaften solitaerer Insekten. Verh Zool-Botan Ges 83:192–201
Rampin C, Cespuglio R, Chastrette N, Jouvet M (1991) Immobilization stress induces a paradoxical sleep rebound in rat. Neurosci Lett 126:113–118
Rattenborg NC, Martinez-Gonzalez D, Lesku JA (2009) Avian sleep homeostasis: convergent evolution of complex brains, cognition and sleep functions in mammals and birds. Neurosci Biobehav R 33:253–270
Rau P (1938) Additional observation on the sleep of insects. Ann Ent Soc Am 13:540–556
Rau P, Rau N (1916) The sleep of insects. An ecological study. Ann Ent Soc Am 13:227–274
Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques an scoring system of sleep stages in human subjects. Brain information service/Brain research institute, University of California, Los Angeles
Retey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP (2005) A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. Proc Natl Acad Sci U S A 102:15676–15681
Rosa RR, Bonnet MH (1985) Sleep stages, auditory arousal threshold, and body-temperature as predictors of behavior upon awakening. Int J Neurosci 27:73–83
Roussel B, Turrillot P, Kitahama K (1984) Effect of ambient-temperature on the sleep-waking cycle in 2 strains of mice. Brain Res 294:67–73
Rusterholz T, Achermann P (2011) Topographical aspects in the dynamics of sleep homeostasis in young men: individual patterns. BMC Neurosci 12:84
Sanford LD, Yang LH, Wellman LL, Liu XL, Tang XD (2010) Differential effects of controllable and uncontrollable footshock stress on sleep in mice. Sleep 33:621–630
Saper CB, Chou TC, Scammell TE (2001) The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 24:726–731
Sauer S, Herrmann E, Kaiser W (2004) Sleep deprivation in honey bees. J Sleep Res 13:145–152
Schaul N, Gloor P, Ball G, Gotman J (1978) The electromicrophysiology of delta waves induced by systemic atropine. Brain Res 143:475–486
Schwierin B, Borbely AA, Tobler I (1996) Effects of N6-cyclopentyladenosine and caffeine on sleep regulation in the rat. Eur J Pharmacol 300:163–171
Sharplin J (1963) Choice of resting stie by notuoidea (Lepidoptera). Ent Mon Mag 99:53–62
Shaw P (2003) Awakening to the behavioral analysis of sleep in Drosophila. J Biol Rhythms 18:4–11
Shaw PJ, Cirelli C, Greenspan RJ, Tononi G (2000) Correlates of sleep and waking in Drosophila melanogaster. Science 287:1834–1837
Siegel JM (2005) Clues to the functions of mammalian sleep. Nature 437:1264–1271
Siegel JM (2009) Sleep viewed as a state of adaptive inactivity. Nat Rev Neurosci 10:747–753
Spiegel K, Tasali E, Leproult R, Van Cauter E (2009) Effects of poor and short sleep on glucose metabolism and obesity risk. Nat Rev Endocr 5:253–261
Stickgold R (2013) Parsing the role of sleep in memory processing. Curr Opin Neurobiol 23:847–853
Strijkstra AM, Daan S (1998) Dissimilarity of slow-wave activity enhancement by torpor and sleep deprivation in a hibernator. Am J Physiol 275:R1110–R1117
Strumwasser F (1971) The cellular basis of behavior in Aplysia. J Psychiatr Res 8:237–257
Szentirmai E, Krueger JM (2006) Obestatin alters sleep in rats. Neurosci Lett 404:222–226
Tafti M, Franken P (2002) Invited review: genetic dissection of sleep. J Appl Physiol 92:1339–1347
Timofeev I, Bazhenov M, Seigneur J, Sejnowski T (2012) Neuronal synchronization and thalamocortical rhythms in sleep, wake and epilepsy. In: Noebels JL, Avoli M, Rogawski MA,

Olsen RW, Delgado-Escueta AV (eds) Jasper's basic mechanisms of the epilepsies 4th edition. NCBI, pp 1–24
Tobler I (1984) Evolution of the sleep process: a phylogenetic approach. Exp Brain Res Suppl 8:207–226
Tobler I, Borbely AA (1986) Sleep EEG in the rat as a function of prior waking. Electroencephalogr Clin Neurophysiol 64:74–76
Tobler I, Borbely AA (1988) Sleep and Eeg Spectra in the Pigeon (Columba, Livia) under Baseline Conditions and after Sleep-Deprivation. J Comp Physiol A 163:729–738
Tobler I, Jaggi K (1987) Sleep and EEG spectra in the Syrian hamster (Mesocricetus auratus) under baseline conditions and following sleep deprivation. J Comp Physiol A 161:449–459
Tobler I, Neuner-Jehle M (1992) 24-h variation of vigilance in the cockroach Blaberus giganteus. J Sleep Res 1:231–239
Tobler I, Stalder J (1988) Rest in the scorpion—a sleep-like state? J Comp Physiol A 163:227–235
Tobler I, Franken P, Alfoldi P, Borbely AA (1994) Room light impairs sleep in the albino rat. Behav Brain Res 63:205–211
Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
Trachsel L, Edgar DM, Heller HC (1991) Are ground squirrels sleep deprived during hibernation? Am J Physiol 260:R1123–R1129
Valatx JL, Bugat R, Jouvet M (1972) Genetic studies of sleep in mice. Nature 238:226–227
van Oort BE, Tyler NJ, Gerkema MP, Folkow L, Blix AS, Stokkan KA (2005) Circadian organization in reindeer. Nature 438:1095–1096
Viola AU, Archer SN, James LM, Groeger JA, Lo JC, Skene DJ, von Schantz M, Dijk DJ (2007) PER3 polymorphism predicts sleep structure and waking performance. Curr Biol 17:613–618
Vyazovskiy VV, Tobler I (2008) Handedness leads to interhemispheric EEG asymmetry during sleep in the rat. J Neurophysiol 99:969–975
Vyazovskiy VV, Welker E, Fritschy JM, Tobler I (2004) Regional pattern of metabolic activation is reflected in the sleep EEG after sleep deprivation combined with unilateral whisker stimulation in mice. Eur J Neurosci 20:1363–1370
Vyazovskiy VV, Ruijgrok G, Deboer T, Tobler I (2006) Running wheel accessibility affects the regional electroencephalogram during sleep in mice. Cereb Cortex 16:328–336
Vyazovskiy VV, Achermann P, Tobler I (2007) Sleep homeostasis in the rat in the light and dark period. Brain Res Bull 74:37–44
Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G (2011) Local sleep in awake rats. Nature 472:443–447
Werth E, Achermann P, Borbely AA (1996a) Brain topography of the human sleep EEG: antero-posterior shifts of spectral power. NeuroReport 8:123–127
Werth E, Dijk DJ, Achermann P, Borbely AA (1996b) Dynamics of the sleep EEG after an early evening nap: experimental data and simulations. Am J Physiol 271:R501–R510
Werth E, Achermann P, Borbely AA (1997) Fronto-occipital EEG power gradients in human sleep. J Sleep Res 6:102–112
Williams HL, Lubin A, Daly RL, Hammack JT, Dement WC (1964) Responses to auditory stimulation sleep loss + EEG stages of sleep. Electroen Clin Neuro 16:269–279
Woelfle MA, Ouyang Y, Phanvijhitsiri K, Johnson CH (2004) The adaptive value of circadian clocks: an experimental assessment in cyanobacteria. Curr Biol 14:1481–1486
Yasenkov R, Deboer T (2010) Circadian regulation of sleep and the sleep EEG under constant sleep pressure in the rat. Sleep 33:631–641
Yasenkov R, Deboer T (2012) Circadian modulation of sleep in rodents. Prog Brain Res 199:203–218
Young R (1935) Sleep aggregations of the beetle, *Altica Bimarginata*. Science 81:435–436

Genetic Dissection of Sleep Homeostasis

Géraldine M. Mang and Paul Franken

Abstract Sleep is a complex behavior both in its manifestation and regulation, that is common to almost all animal species studied thus far. Sleep is not a unitary behavior and has many different aspects, each of which is tightly regulated and influenced by both genetic and environmental factors. Despite its essential role for performance, health, and well-being, genetic mechanisms underlying this complex behavior remain poorly understood. One important aspect of sleep concerns its homeostatic regulation, which ensures that levels of sleep need are kept within a range still allowing optimal functioning during wakefulness. Uncovering the genetic pathways underlying the homeostatic aspect of sleep is of particular importance because it could lead to insights concerning sleep's still elusive function and is therefore a main focus of current sleep research. In this chapter, we first give a definition of sleep homeostasis and describe the molecular genetics techniques that are used to examine it. We then provide a conceptual discussion on the problem of assessing a sleep homeostatic phenotype in various animal models. We finally highlight some of the studies with a focus on clock genes and adenosine signaling molecules.

Keywords Sleep homeostasis · Genetics · QTL · Polymorphism · Knockout · Sleep deprivation · EEG delta power · Sleep need · Clock genes · Adenosine

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Contents

1 Introduction

Despite decades of research aimed at elucidating sleep and wake regulation in mammals, little is known about the identity of genes that regulate sleep, a fundamental behavior that in humans occupies about one third of our lifespan. The various aspects of sleep differ in their regulation and interact with each other and with the environment, each of them being under the control of a multitude of genes. Therefore, each component of sleep must be considered a complex trait. Over the past 70 years, abundant evidence has accumulated demonstrating that many aspects of sleep and the electroencephalogram (EEG) are strongly determined by genetic factors (Andretic et al. 2008). In humans, the earliest observations came from twin studies showing that sleep patterns and sleep habits within monozygotic twins have a higher concordance than within dizygotic twin pairs or unrelated subjects with heritabilities ranging from 40 to 60 % (Geyer 1937; Linkowski 1999). More recent twin studies showed that quantitative EEG features, with heritability estimates of well over 80 % for specific frequency components, rank among the most heritable traits in humans (Van Beijsterveldt et al. 1996; Stassen et al. 1999; Ambrosius et al. 2008; De Gennaro et al. 2008). After these initial observations in humans, most subsequent genetic sleep and EEG studies have been performed in mice. In the 1970s, Jean-Louis Valatx introduced sleep genetics in the mouse at the Université

Claude Bernard and observed profound differences in sleep among inbred strains of mice (Valatx et al. 1972; Valatx and Bugat 1974). Like in humans also in the mouse additive genetic factors account for about half of the variance in the amount and distribution of sleep and >80 % for a variety of EEG traits (Andretic et al. 2008). Despite numerous reports on the genetic determinants of sleep and the EEG, remarkably little progress has been made in isolating the genes or gene pathways underlying these traits. The development of recent technologies and statistical tools has greatly facilitated genetic studies of sleep.

One important aspect of sleep, that will be the focus of this review, concerns its homeostatic regulation. Like other physiological variables that are homeostatically regulated (e.g., blood glucose levels, body temperature, food intake), the concept of homeostasis can be applied to sleep, since it seems essential for optimal functioning of the organism and lack of sleep is compensated by sleeping more and/or sleeping deeper. This sleep homeostatic process is thought to keep a level of sleep pressure within physiological range; i.e., sufficiently low to allow the brain and organism to operate in an appropriate manner. However, the neurophysiological function of sleep and the variables that are homeostatically defended still remain elusive, and is one of the main topics of current sleep research. Our modern 24/7 society, in which professional and social activities increasingly prevail to the detriment of sufficient good quality sleep, comes with a cost for health and well-being both to the individual and to society (Bixler 2009). Therefore, finding clues about the genetic and molecular processes defining and controlling the need for sleep could be beneficial to improve human's well-being and performance. Gaining insight into the molecular pathways underlying sleep homeostasis requires a multidisciplinary approach, using a combination of genetic and molecular genetic approaches making use of available animal models and analytical tools. This review focuses on the use of genetic and molecular techniques to study sleep homeostasis in three model organisms; i.e., human, mouse, and fly. Other aspects of sleep will not be discussed here. In the following, we first describe the concept of sleep homeostasis (Sect. 2), then we provide a background of the genetic approaches used to study sleep homeostasis in model organisms (Sect. 3). The subsequent sections present studies on some of the gene pathways that have been implicated in sleep homeostasis, with emphasizes on circadian clock genes and components of the adenosine pathway. Section 8 briefly discusses the molecular genetic screens that have highlighted potential homeostatic molecules and provides an example of a combination of several genetic techniques that led to the discovery of a now established marker of sleep homeostasis, *Homer1a*.

2 Sleep and its Homeostatic Regulation

The notion of homeostasis was first introduced by Claude Bernard in 1926 and further developed by Walter Cannon, as the property of a system to maintain its internal environment stable and constant allowing an organism to function

optimally over a broad range of environmental conditions (Canon 1915). Homeostatic regulation involves three essential parts: a sensor that measures the controlled variable, an integrator that processes information and compares the variable to a set point (or rather the optimal range within which the controlled variable can vary), and effectors that respond to the commands of the integrator when the level of the variable deviates from set point. None of these three parts are known with certainty in sleep because we do not know what function(s) sleep fulfills. Although we have identified variables that reliably track the prior sleep–wake distribution (see below), it is likely that these are not themselves the homeostatically defended variables but rather reflect an underlying process. Moreover, sleep homeostasis has distinct local and use dependent properties suggesting that sleep's function(s) is a property of neuronal assemblies rather than involving the whole organism or even the whole brain (Krueger et al. 2008). Therefore, the homeostatic control of sleep might, like that for circadian rhythms, operate at cellular-molecular level (Hinard et al. 2012).

2.1 Homeostatic and Circadian Control of Sleep

Homeostatic sleep pressure (*aka* sleep propensity or sleep need) accumulates during wakefulness and decreases during sleep. The increased need for sleep that accompanies sleep loss seems to be compensated by sleeping longer and/or intensifying sleep leading to the return to set point. Sleep homeostasis is primarily studied by performing sleep deprivation (SD) experiments although in a few studies the effects of a nap (Werth et al. 1996; Vienne et al. 2010) and the effects of spontaneous waking episode durations (Franken et al. 2001) on sleep pressure have been studied. The effects of SD can be assessed on a variety of sleep parameters.

The control of sleep cannot solely be explained by homeostatic control, as it involves at least one other main process: a circadian process that determines the time of day at which sleep occurs (Borbély 1982; Daan et al. 1984). In mammals, the circadian control is orchestrated by the suprachiasmatic nucleus (SCN) of the hypothalamus (Klein et al. 1991) which is considered the master circadian clock. The output of this clock gives time context to most physiological processes and behaviors including sleep, and ensures the proper entrainment of internal rhythms to the daily light–dark cycle. The interaction between the homeostatic and the circadian process was described first in the two-process model of sleep regulation (Borbely 1982; Daan et al. 1984). It now has become established that their close interaction determines the duration, the quality, and the quantity of sleep and that it enables us to stay awake and alert through the day despite an increasing need for sleep and to sleep throughout the night despite a decreasing need for sleep (Dijk and Franken 2005). Despite this important interaction between the two, evidence has shown that each of the processes develops independently (Trachsel et al. 1992; Dijk and Czeisler 1995; Easton et al. 2004; Larkin et al. 2004; for review see Franken 2013).

2.2 NREM Sleep Homeostasis

The homeostatic regulation of non-rapid eye movement (NREM) sleep has been extensively studied in mammals; it consists of an increase in both the duration and the depth or "intensity" of NREM sleep after extended periods of wakefulness. The most widely used index to quantify homeostatic sleep need relates to the prevalence and amplitude of EEG slow waves (or delta waves; 0.75–4.5 Hz), quantified by the Fourier transformation as EEG delta power (*aka* slow-wave activity or SWA). Changes in EEG delta power follow the sleep–wake distribution (Tobler and Borbély 1986; Dijk et al. 1987; Franken et al. 1991a, 2001). EEG delta power in NREM sleep is high at the beginning of the sleep episode, and decreases with the duration of time spent asleep. The declining trend of EEG delta power over the course of a sleep episode is thought to reflect the homeostatic decline of sleep propensity. After an episode of extended wakefulness, EEG delta power in subsequent NREM sleep is high and its magnitude depends on the duration of prior wakefulness. The changes in EEG delta power are highly reliable and can be predicted mathematically solely based on the sleep–wake distribution both under baseline conditions and after SD (Franken et al. 1991b, 2001, 2006; Huber et al. 2000; Achermann and Borbely 2003; Deboer 2009). The fact that most of the variance in EEG delta power can be attributed to the sleep–wake distribution contributed to the notion that this variable reflects a homeostatic process related to NREM sleep. In a functional context, NREM sleep with high levels of EEG delta power is considered especially recuperative not only for the brain but also for the body (Tasali et al. 2008).

Besides its intensity, also the time spent in NREM sleep seems to be homeostatically regulated as it tends to increase after SD. However, sleep duration also importantly depends on the circadian phase at which sleep occurs, in contrast to EEG delta power of which the dynamics are little affected by the circadian process (Dijk and Czeisler 1995). Another difference between the homeostatic regulation of EEG delta power and NREM sleep duration is that the dynamics of the former are fast (i.e., hours), while rebounds in the latter can be delayed and span over several days (e.g., Franken et al. 1991a). The homeostatic regulation of NREM sleep duration has received very little attention thus far. This is also reflected by current hypotheses on sleep function that focus exclusively on the sleep–wake dependent dynamics of EEG delta power while ignoring time spent in sleep (e.g., Tononi and Cirelli 2006). Interestingly, while EEG delta power or other electrophysiological correlates of sleep need have not been identified in *Drosophila melanogaster* and although sleep after enforced wakefulness in the fly also deepens judged on increased arousal thresholds and increased consolidation, the homeostatic regulation of sleep is derived mainly from the time spent asleep (Huber et al. 2004).

2.3 REM Sleep Homeostasis

Even though, at least in rodents, the amount of REM sleep is usually more accurately regulated than the amount of NREM sleep, the question whether REM sleep is homeostatically regulated remains a topic of debate. Support for a homeostatic regulation of REM sleep comes from studies in cats, rats, mice as well as humans (Benington et al. 1994; Endo et al. 1997; Rechtschaffen et al. 1999; Franken 2002; Amici et al. 2008). Although in all species listed REM sleep pressure, quantified as the number of attempts to enter REM sleep, does increase when REM sleep is selectively deprived of (Benington et al. 1994; Endo et al. 1998; Ocampo-Garcés et al. 2000), an increase in REM sleep time during recovery sleep that is proportional to the loss of REM sleep during a preceding deprivation, is only consistently observed in some animal studies (see Franken 2002 for a review). Unlike NREM sleep, a loss of REM sleep seems to be primarily compensated by spending more time in REM sleep, although EEG measures indicative of the depth of REM sleep have been proposed (Borbély et al. 1984; Roth et al. 1999). While such observations do suggest that REM sleep amount is homeostatically regulated, this has received little attention in genetic studies and unraveling the molecular underpinning of the NREM sleep homeostatic process has been a main focus. Nevertheless, several KO mouse studies found evidence for clock genes regulating the degree by which REM sleep increases after SD (see Sect. 5).

3 Approaches and Techniques to Study Sleep Genetics

3.1 Forward Genetics

To study the genetics of sleep, three complementary approaches are generally considered: forward, reverse, and molecular genetics (Fig. 1). Conceptually, the forward genetic approach is the most powerful strategy for the identification of novel genes and gene pathways involved in any biological process. Forward genetics is a classical genetic approach starting from the observation of a particular phenotype within an organism and comprises several means to map and identify the gene or set of genes that are responsible for this precise phenotype. Examples of forward genetic approaches in animals are mutagenesis screens and quantitative trait loci (QTL) analysis. QTL analysis has been proposed to dissect complex traits because with this approach, natural allelic variation of genes with small effect can be mapped (Lander and Botstein 1989; Darvasi 1998; Belknap et al. 2001; Flint and Mott 2001). QTL analysis has been used in several segregating populations including intercross and backcross, advanced intercross and backcross panels, and notably in genetic reference populations (GRP) such as recombinant inbred (RI) stock (Darvasi 1998; Talbot et al. 1999). The best characterized GRP is the BXD

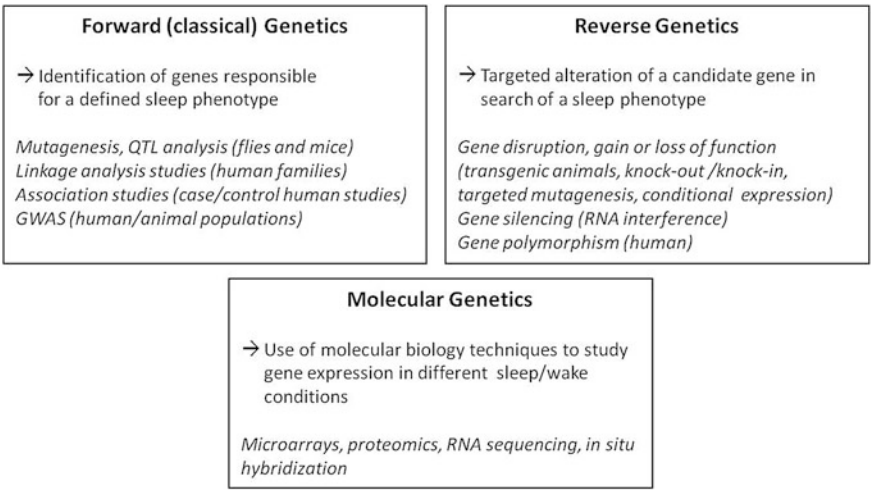

Fig. 1 Genetic approaches used in sleep homeostasis research. For each of these approaches, different techniques can be employed in different animal species to bring information about the involvement of genes in sleep and its homeostasis. The three approaches are complementary and should be combined to decipher the molecular pathways of sleep homeostasis

RI set derived from two inbred strains: C57BL/6 J and DBA/2 J. The BXD set has been used for decades to map the genetic basis of complex traits (see www.genenetwork.org for the accumulated data). The first forward genetic study that specifically assessed as a trait in the mouse was performed in the BXD set (Franken et al. 2001). Another example of GRP is the Collaborative Cross, a more recent mouse population with high allelic diversity that is being constructed using a randomized breeding design that systematically outcrosses eight founder strains, followed by inbreeding to obtain new RI strains (Philip et al. 2001). In *Drosophila* the first mutagenesis screen for sleep phenotypes was performed in 2003 (Cirelli 2003). Using DNA alkylating agents such as ethyl methane sulfonate, or DNA transposable elements, random mutations are induced throughout the genome. With high-throughput screening of thousands of offspring for dominant, semi-dominant, or recessive mutations, a major effect on a given trait can be identified. Thus, forward genetics can be used to establish causal relationship between the function of individual genes and otherwise complex phenotypes. However, genetic screens in this approach are for fully penetrant dominant and recessive mutations and therefore cannot identify small effect sequence variations that may turn out to be essential for some aspects of the phenotype. Thus because of advantages and disadvantages associated with each of these two approaches, QTL and mutagenesis should be viewed as complementary (Belknap et al. 2001).

In humans, traits of interest are generally examined by linkage analyses. Linkage studies investigate shared chromosomal fragments among members of a family who manifest the trait of interest or the disease. By analyzing the co-segregation of the trait and chromosomal markers, it may be possible to

statistically identify chromosomal loci "linked" to the trait. However, linkage studies are limited by the availability of family-based samples, and rely on the observation of heritability of the trait of interest. In comparison, association studies of genetically complex traits require larger samples and involve comparisons between cases and controls with respect to selected polymorphisms (Altshuler et al. 2008; Chiang et al. 2009). In genome-wide association studies (GWAS) the concept of association study is extended to the whole genome, with the idea to observe the segregation of many polymorphisms with the disease or the trait. Thus, the relative impact of different genomic regions can be assessed simultaneously in the same sample. Despite initial excitement the loci identified in GWAS studies have, in general, weak additive power, explaining only a small portion of the narrow-sense heritability reported for a given phenotype. This suggests that rare rather than the common variants interrogated in a GWAS, underlie the phenotype of interest. Moreover, most reported loci are noncoding and thus not immediately informative and GWAS results not always replicate across studies and populations leading to false positives (Ward and Kellis 2012).

The GWAS can also be applied to outbred mouse populations (Yalcin et al. 2010). Increased recombination in outbred populations is expected to provide greater mapping resolution than traditional inbred line crosses, improving prospects for identifying the causal genes for a trait. However, outbred populations are not a GRP and thus each individual is genetically unique and has to be genotyped individually. This also limits the number of phenotypes that can be obtained for a given genotype which is another advantage of using GRPs.

3.2 Reverse Genetics

In contrast to forward genetics, in which the strategy is to go from the observed phenotype to the underlying genotype, reverse genetics starts with a disrupted or altered gene of interest and examine its effect on a phenotype or phenotypes of interest. In humans, reverse genetic studies most often concern natural occurring functional polymorphisms while the use of animal models allows for targeting specific genes. Transgenic animals can be used to study the consequences of overexpression, ectopic expression, time- and tissue-specific expression, and gain or loss of function of a specific gene. To date, a large number of studies in sleep genetics have utilized reverse genetic approaches by knocking-out a gene of interest (see Sect. 5.1). The delineation between reverse and forward genetic approaches is not a formal one and depends on the scale at which they are used. Transgenic strategies can also been used in forward genetic studies, in which hundreds of mutated or knockout (KO) lines of mice (Knight and Abbott 2002), or flies (Cirelli 2003) are screened. The International Knockout Mouse Consortium is currently creating a collection of mouse in which all protein-coding genes are mutated and will therefore provide a population of animals for genome-wide screens (Ringwald et al. 2011).

3.3 Molecular Genetics

Molecular genetics is an approach that evaluates changes in gene expression related to the trait of interest; it is an unbiased method that makes use of several techniques such as DNA microarrays, proteomics, and RNA sequencing. Molecular approaches in sleep studies are based on the assumption that the expression of genes change as a function of time spent awake or asleep (Cirelli et al. 2004; Mackiewicz et al. 2009; Thompson et al. 2010). Rhyner et al. were the first to use a molecular approach to identify genes that change their expression after SD in the rat, and identified the protein neurogranin to be decreased in the rat forebrain after 24 h of SD (Rhyner et al. 1990). These methods have been helpful in identifying the brain expression of genes involved in sleep or modulated by sleep (see Sect. 8). However, these approaches cannot reveal a causal relationship between a gene or a set of genes and a particular behavior or phenotype. For example, a gene that does not show transcriptional modification may nonetheless play an important role in the process under investigation. On the other hand, a transcript that does increase with increased sleep need might merely be driven by the sleep–wake distribution while not playing a role in the homeostatic sleep process itself.

It is clear that the above approaches are complementary; e.g., the function of candidate genes identified with QTL or molecular genetics approaches have to be confirmed in KO animals (an example is provided in Sect. 8.1). Future efforts should therefore combine genetics approaches in animal models and GWAS in humans to facilitate uncovering the molecular pathways that underlie sleep homeostasis. However, other approaches and techniques will remain important in making progress in elucidating the complex physiology of sleep; genetic dissection of sleep can be used in conjunction with state-of-the-art electrophysiological, neuroanatomical and pharmacological techniques already used with great success in sleep research.

4 In Search for Sleep Homeostatic Genes: Defining the Phenotype

A sleep homeostatic gene could be defined as a gene that modifies the sleep–wake dependent dynamics of EEG delta power or a gene that affects the (compensatory) increase in NREM or REM sleep duration after SD. Establishing whether a gene variant affects a sleep homeostasis process is, however, not always straightforward and several considerations have to be taken into account in the analysis. Here we illustrate some of the general problems that can occur with interpreting the results of SD studies that should be considered before claiming a homeostatic phenotype is observed.

Although, sleep homeostatic processes could, in principle, be assessed and quantified under baseline conditions, usually sleep homeostatic responses are

studied after experimentally challenging sleep need through; e.g., keeping subjects awake for a certain duration at a time-of-day sleep is present under undisturbed baseline conditions. In most studies, sleep variables measured during recovery sleep after enforced waking are then contrasted to the individual levels reached in baseline. Subsequently, these relative changes are compared between genotypes to assess the effect of a disrupted or mutated gene of interest on sleep homeostasis (Fig. 2a). A slightly more elaborate variant of such analysis are the so-called "gain-loss" time course analyses in which the sleep loss incurred over the course of a SD is analyzed by accumulating the differences of sleep observed during the SD minus the sleep duration observed during the same time-of-day during baseline (Fig. 2b′). This accumulated sleep deficit then serves as the starting point of the sleep gained during the recovery period following a SD and is assessed in the same way (i.e., as relative differences from matching times during baseline). Genotype differences in 'gain-loss' dynamics are then taken as evidence of an altered homeostatic regulation of sleep. An important short-coming of such analyses is that they implicitly assume that the sleep obtained during baseline is the amount a subject "needs" or, in other words, the duration of sleep that is homeostatically defended. For instance, the deficit in sleep duration in the gain-loss analyses introduced above exclusively reflects the sleep duration obtained during the baseline period the SD took place (given that no sleep is obtained during the SD protocol). Also the recovery dynamics are obtained by contrasting recovery values to corresponding baseline values. In the hypothetical example shown in Figs. 2b and 2b′, the recovery dynamics of sleep is exactly the same; i.e., each hour the same duration of *extra* sleep is obtained making the recovery curves run in parallel. Nevertheless, a researcher can claim the discovery of a homeostatic phenotype because of statistical genotype differences that, in this case, are due only to a difference of sleep expressed during baseline at the time SD was performed. In another example, recovery was made to be exactly proportional to the sleep duration the animal was deprived of and this amount of *extra* sleep was linearly distributed of the 18 h depicted (example in Fig. 2b′). As a result, in this exercise, recovery is "complete" by hour 24 (i.e., after 18 h of recovery) reaching the zero deficit level in both genotypes. Nevertheless, a researcher can again claim that homeostatic regulation is different between genotypes because the SD resulted in different relative deficits and the slopes of the gain process differed, while it could equally be claimed that recovery of sleep time lost is perfect and not different in both because in one case more sleep was deprived of and thus a higher pressure for sleep was accrued leading to more extra sleep. Many other scenarios could be construed pointing out these or related problems such as the so-called "ceiling effect." This effect is sometimes alluded to account for a smaller increase attained during recovery at times-of-day when during baseline the subject already sleeps a lot. It is clear, and all will agree, that the level of a sleep variable expressed during baseline cannot be attributed to homeostatic need alone. For example, in a study examining sleep need in short and long sleepers that differed in habitual sleep duration by more than 3 h, it was concluded that the dynamics of the sleep

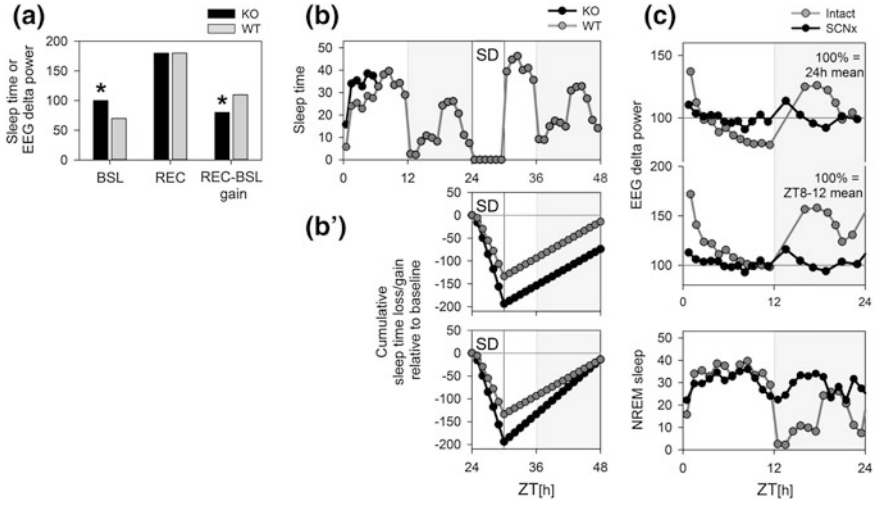

Fig. 2 Conceptual issues when assessing a sleep homeostatic phenotype. (*Panel a*) Sleep regulation in mice carrying a targeted deletion of a gene (i.e., knockout or KO) is compared to that in wild-type (WT) controls by submitting mice of both lines to a sleep deprivation (SD). Time spent asleep during the recovery period (REC) or the level of EEG delta power reached after the onset of recovery sleep was higher than in baseline (BSL) in both genotypes but levels reached did not differ between them. Nevertheless, by contrasting the values obtained during recovery to those obtained during baseline (REC-BSL gain), a significant (*) difference in gain was observed. The gain difference in this hypothetical example must, however, be ascribed to the differences in baseline. (*Panels b*) In another example, KO mice differed only from WT mice in the first 6 h of the baseline (ZT0-6; top panel) during which KO mice slept 1 h more. During the remainder of the experiment the two genotypes had identical amounts of sleep. The effect of SD was analyzed with a loss/gain analysis by accumulating the sleep time lost during the SD (−140 min in WT) and the extra sleep obtained during recovery from a 6 h SD (+200 min in both genotypes). Because of the baseline difference in sleep amount at the time the SD was performed the following day, KO mice start with a 60 min higher sleep deficit at the start of recovery sleep. Although the extra sleep obtained during recovery sleep did not differ (*parallel gain curves*) KO maintain a deficit. In (*Panel b′*) a scenario is depicted where both genotypes fully compensate for their differing sleep time lost during SD; i.e., reaching 0 levels within the 18 h of recovery. Does sleep homeostasis differ (*steeper gain curve*) or not (same end point)? Baseline and recovery data for b′ not included in *upper panel*. (*Panels c*) The sleep–wake distribution (*lower panel*) drives changes in EEG delta power such that during periods when NREM sleep is prevalent (light period ZT0-12) EEG delta power decreases in an exponential fashion while during period of wakefulness (first half of the dark period; ZT12-18) EEG delta power in subsequent NREM sleep is elevated. In SCN-lesioned (SCNx) animals that sleep more and in which the distribution of NREM sleep over the day is strongly reduced, EEG delta power can be expected to be low and its time course flat over a 24 h *baseline* recording. Taking the 24 h mean value of EEG delta power as a reference (100 % *upper panel*), as is often done, results in overall higher relative values of EEG delta power in SCNx mice such as in *baseline* (e.g., ZT6-12) and also after SD (not illustrated) compared to intact mice that can lead to erroneous conclusions concerning homeostatic sleep need. We propose to take the EEG delta power values reached during the last 4 h of the main rest phase (ZT8-12) as a reference (100 % *middle panel*)

homeostat did not differ and that short sleepers somehow could resist higher levels of sleep pressure (Aeschbach et al. 1997, 2001).

The problem becomes even more complex when the variable cannot be directly analyzed in absolute terms (i.e., in the units they are measured) because, due to a range of confounds (e.g., electrode placement, impedance) variability among individuals is large thereby decreasing statistical power. Quantitative EEG variables are therefore often expressed relative to an individually calculated reference value to reduce variability among subjects. Differences in absolute levels should also be corrected for variables for which only the sleep–wake dependent changes are considered informative. Our genetic analyses of the sleep–wake dependent relative changes in EEG delta power and of the contribution of EEG delta power to NREM sleep EEG revealed that these two aspects are under the control of different genetic factors (Franken et al. 2001; Maret et al. 2005). Similarly, EEG delta power contributes more prominently to the NREM sleep EEG in female compared to male mice; nevertheless, the sleep–wake dependent dynamics of the changes in EEG delta power differ with sex such that the build-up in females is slower than in males, and therefore higher absolute EEG delta power not necessarily reflect higher homeostatic sleep need (Franken et al. 2006). Studies in humans arrive at similar conclusions. EEG analyses in subjects carrying specific polymorphisms has demonstrated that large genotype effects on the prevalence and amplitude of EEG delta waves (absolute values) do not necessarily translate in differences in the sleep–wake dependent relative changes in EEG delta power (i.e., homeostasis; reviewed in Franken 2012). As a last example illustrating this duality between these two aspects of EEG delta power, the effect of benzodiazepines can be mentioned. These sleep-promoting drugs are known to reduce EEG delta power while leaving the sleep–wake dependent dynamics unaffected (Borbely and Achermann 1991). Therefore, one should be cautious with making claims on sleep homeostasis and sleep depth based on absolute EEG values. Assessing other, non-EEG indexes of NREM sleep depth or quality such as the fragmentation of NREM sleep (Franken et al. 1991a, 1999) or arousal thresholds (Neckelman and Ursin 1993; Wimmer et al. 2012) could be used to strengthen such claims.

When investigating the homeostatic regulation of sleep, the relative changes in EEG delta power related to the sleep–wake distribution are analyzed. The individual reference value for EEG delta power should be chosen such that effects of eventual differences in the sleep–wake distribution and sleep duration do not affect the result. As the sleep–wake distribution is the main determinant of the changes in EEG delta power, genotype differences in sleep duration as well as sleep distribution can greatly impact average levels of EEG delta power while not (necessarily) impacting the dynamics of the underlying homeostatic process. This can be illustrated in SCN-lesioned animals (Trachsel et al. 1992). In our hypothetical example (Fig. 2c), removing the SCN results in an increase in sleep and in a "flat" distribution of sleep over the 24 h day mainly due the lack of the consolidated period of wakefulness after dark onset. The bout of spontaneous wakefulness results in high levels of EEG delta power in subsequent NREM sleep in the intact animals, levels that are never reached in SCN-lesioned animals. Therefore, when

taking the 24 h mean value of EEG delta power as a reference, as is often done, this reference value will be higher in the intact animals compared to the same reference in the arrhythmic animals. As a result, the relative values calculated using this reference, will be lower in the intact animals and when compared to the lesioned animals could lead to erroneous statements concerning sleep homeostasis because the difference in the level in EEG delta power reached after SD are an artifact of selecting the reference. As an alternative, we have proposed to use the mean EEG delta power reached in the last portion (4 h) of the rest phase (or light phase in nocturnal species) as a reference (Franken et al. 1999). Levels reached at this time are less dependent on eventual differences in the sleep–wake distribution because EEG delta power decreases exponentially and EEG delta power differences at sleep onset gradually disappear over the course of the rest phase. In our hypothetical case of the SCN-lesioned animal, EEG delta power does not appreciatively deviate from this low level (Fig. 2c).

Another issue concerning the interpretation of EEG delta power seen in the literature is to contrast EEG delta power measured after SD to its value at corresponding clock time during baseline. Already minor genotype differences in the sleep–wake distribution during baseline can lead to significant differences in EEG delta power. Therefore, by expressing values reached after SD as a percentage of values reached during particular times during baseline can lead to wrong conclusions. To circumvent the problem of having to contrast values obtained after a SD to a baseline reference, "dose–response" experiments could be considered. In such studies, SDs of different durations could be used to quantify directly the dynamics of the relationship between the time animals were kept awake and the response variable (sleep duration, EEG delta power etc.; e.g., Tobler and Borbely 1986; Franken et al. 2001; Seugnet et al. 2006). To quantify the relationship between the sleep–wake distribution and EEG delta power, computer simulations can be used as an alternative approach (Franken et al. 2001).

In conclusion, the definition of an altered sleep homeostasis is not trivial. Besides some of the conceptual issues outlined above, differences in methods to perform SD such as the sleep time allowed during the SD, recording and analyzing the EEG further add to the problem of unambiguously establishing whether a genotype difference in the response to sleep loss qualifies as a homeostatic sleep phenotype.

Many different cells, molecules, and signaling pathways have been investigated through reverse genetic studies for their possible role in the control of sleep homeostasis (Table 1). In the Sect. 5 through 8, we give an overview of the pathways that have been linked to sleep homeostasis, with an emphasis on clock genes and adenosine. The list provided is, however, non-exhaustive and many other systems are currently under investigation. Even though these studies brought essential information in the understanding of sleep homeostasis, a unifying picture on its genetic control has yet to emerge.

Table 1 Genes investigated through reverse genetic studies for their involvement in sleep homeostasis

Family	Gene	Species	Homeostatic phenotype	References
Clock genes	*Clock*	Mouse	Yes	Naylor et al. 2000
		Fly	Yes	Shaw et al. 2002
	Bmal1	Mouse	Yes	Laposky et al. 2005
	Cycle	Fly	Yes	Shaw et al. 2002
	Npas2	Mouse	Yes	Franken et al. 2006
	Cry1, Cry2	Mouse	Yes	Wisor et al. 2002
	Dbp	Mouse	No	Franken et al. 2000
	Per1, Per2	Mouse	No	Kopp et al. 2002
		Mouse	No	Shiromani et al. 2004
		Fly	Yes	Shaw et al. 2002
	Per3	Mouse	No	Shiromani et al. 2004
		Mouse	Yes	Hasan et al. 2011
		Mouse	Yes	Hasan et al. 2012
		Human	Yes	Viola et al. 2007
	2-Dec	Mouse	Yes	He et al. 2009
Adenosine	A_1R	Mouse	No	Stenberg et al. 2003
		Mouse	Yes	Bjorness et al. 2009
		Mouse	Yes	Halassa et al. 2009
	A_2R	Mouse	Yes	Urade et al. 2003
	dAdoR	Fly	No	Wu et al. 2009
	Adk	Mouse	Yes	Palchykova et al. 2010
	CD73	Mouse	Yes	Zielinski et al. 2012
Neurotransmitters	*COMT*	Human	No	Bodenmann et al. 2009
		Human	Yes	Goel et al. 2011
	GABAR	Mouse	No	Winsky-Somerer et al. 2009
		Mouse	No	Vienne et al. 2010
Ion channels	*Sh*	Fly	No	Cirelli et al. 2005
	Sss	Fly	Yes	Koh et al. 2008
	Hk	Fly	No	Bushey et al. 2007
	Kcna2	Mouse	No	Douglas et al. 2007
Signaling pathways	*BDNF*	Human	Yes	Bachman et al. 2012
Stress and immunity	*BiP*	Fly	Yes	Naidoo et al. 2005
	Hsp83	Fly	Yes	Shaw et al. 2002
Synaptic plasticity	*Homer1*	Mouse	No	Maret et al. 2007
	Homer	Fly	Yes	Naidoo et al. 2012
	Homer1a	Mouse	No	Naidoo et al. 2012

The current list is non-exhaustive and presents only the studies that were discussed in the chapter (see Sects. 5–8). The observation of an altered homeostatic sleep phenotype (4th column of the table) is based on the conclusions of the authors of the cited publications. See text for details

5 Circadian Clock Genes

Although the genes referred to as clock genes are involved in many pathways they are best known (and named) for their role in circadian rhythm generation. Clock genes are transcriptional regulators engaged in negative feedback loops that underlie the molecular circuitry of the circadian clock machinery (Ko and Takahashi 2006). Positive elements of this feedback loop are three factors: CLOCK, NPAS2, and BMAL1. NPAS2::BMAL1 and CLOCK::BMAL1 heterodimers can drive transcription of many genes including the *Period* (*Per1* and *-2*) and *Cryptochrome* (*Cry1*, and *-2*) genes. PER::CRY protein complexes suppress CLOCK/NPAS2::BMAL1-mediated transcription and thus their own transcription thereby constituting the negative elements in the feedback loop. Additional interactions between these core clock genes and other actors (e.g., REV-ERBα, RORα) at the level of transcription, translocation back into the nucleus, post-translational modifications add further complexity and stability. In *Drosophila*, the molecular oscillator relies on very similar timing systems using orthologs to the mammalian clock genes (Benito et al. 2007). The central autoregulatory feedback loop is composed of the two factors CLOCK and CYCLE, which are the homologues of the mammalian CLOCK and BMAL1, respectively. The CLOCK::CYCLE heterodimers activates the transcription factors PERIOD and TIMELESS which act as negative regulators like the mammalian PER and CRY proteins, respectively (Tomioka and Matsumoto 2010).

The circadian process and the homeostatic process appear independent (for review see Franken 2013). Rendering animals arrhythmic through lesioning the SCN (Trachsel et al. 1992; Easton et al. 2004) or a light pulse (Larkin et al. 2004), did not affect the increase in EEG delta power after SD. Moreover, studies in humans showed that the sleep–wake dependent dynamics of EEG delta power are little affected by circadian factors (Dijk and Czeisler 1995). Analyses of sleep homeostasis in humans, mice, and flies carrying polymorphism or targeted disruptions of clock genes demonstrate, however, that at least at the molecular level, circadian rhythms and sleep homeostasis are difficult to dissociate (Shaw and Franken 2003; Franken and Dijk 2009). In the following, we will discuss the different clock gene mutants/polymorphisms that have been studied and suggesting a non-circadian role of clock genes in sleep homeostasis.

5.1 Reverse Genetic Studies for Clock Genes

Clock is the first circadian gene identified in a mammal (Vitaterna et al. 1994) and subsequently cloned (Antoch et al. 1997; King et al. 1997). The *Clock* mutation ($Clock^{\Delta/\Delta}$) affects numerous aspects of circadian rhythmicity, including a lengthened circadian period. *Clock* was also one of the first clock genes for which a role in sleep homeostasis has been claimed (Naylor et al. 2000). Under baseline conditions,

Clock$^{\Delta/\Delta}$ mice showed decreased NREM sleep, associated with a reduction in NREM sleep episode length. When challenged with a 6 h SD, *Clock*$^{\Delta/\Delta}$ mice showed a normal NREM sleep rebound but a reduced rebound in REM sleep. The authors suggested that NREM sleep homeostasis was affected by the *Clock* mutation, because NREM sleep delta energy was reduced both during baseline and during recovery. Because this measure is a function of the total time spent in NREM sleep, the difference has, however, to be largely attributed to the fact that these mice slept less. Moreover, when sleep homeostasis was evaluated according to the time course of EEG delta power, no genotype differences could be observed. Therefore, it remains unclear whether the *Clock* mutation affects NREM sleep homeostasis. The altered relative increase in REM sleep, which could not be explained by differences in REM sleep amount in baseline, points to an altered homeostatic regulation of REM sleep. In flies, the mutation of the *Drosophila Clock* homolog mildly affects baseline sleep as well as the response to SD (Shaw et al. 2002). It remains to be determined whether *Clock* KO mice have a sleep homeostatic phenotype.

In addition to abolishing circadian rhythms in overt behaviors, targeted disruption of *Bmal1* leads to profound differences in sleep (Laposky et al. 2005). Under baseline conditions, *Bmal1*$^{-/-}$ mice showed attenuated amplitude of the distribution of sleep and wakefulness across the 24 h day as well as elevated NREM and REM sleep amounts. Moreover, this increase in sleep time was accompanied by a more fragmented sleep. The authors found that sleep intensity, determined as the average of absolute levels of EEG delta power in baseline, was increased in *Bmal1*$^{-/-}$ mice, a surprising finding given that sleep fragmentation and intensity are usually inversely correlated (Franken et al. 2001). To assess genotype effects on the homeostatic regulation the relative, sleep–wake dependent changes in EEG delta power were analyzed in baseline and after a 6 h SD. As normalization the averaged 24 h baseline level was used. With this normalization higher than wild-type (WT), EEG delta power levels were reached in the light period and lower values in the dark period of baseline. This time course can serve as an example of the problem that exists with the use of this reference value (Fig. 2c), especially because *Bmal1*$^{-/-}$ mice sleep overall more and lack the sustained period of wakefulness in the first half of the dark period. As a result, levels of homeostatic sleep pressure can be expected to be constitutively low in *Bmal1*$^{-/-}$ mice, consistent with the lower levels of sleep consolidation observed. Nevertheless, the relative increase in EEG delta power was reduced pointing to slower build-up of homeostatic sleep need.

An extreme sleep homeostatic phenotype was observed in *Cycle* mutants, the fly homolog of *Bmal1*. *Cycle* mutant flies showed an exaggerated sleep rebound after SD and died after 10 h of SD (Shaw et al. 2002). This was the first study to show a vital role for sleep in flies. The combination of circadian disruption and alterations in the response to SD in *Bmal1*$^{-/-}$ mice and in *Cycle* mutant flies supports the notion that this clock gene plays a role in both circadian and sleep homeostatic processes.

In mammals, CLOCK is the main component of the circadian machinery in the SCN and peripheral organs, whereas in peripheral brain regions (i.e., peripheral to the SCN), it is substituted by its paralog NPAS2. CLOCK and NPAS2 are similar in amino acid sequence, share BMAL1 as an obligate partner, bind to the same DNA recognition element, are suppressed by CRY proteins, and commonly depend on favorably reducing ratio of NAD factors (Rutter et al. 2001). Because NPAS2 acts both as a sensor and an effector of intracellular energy balance, and because sleep is thought to correct energy imbalance incurred during waking, *Npas2* might be a candidate for a sleep homeostatic gene. In contrast to $Clock^{\Delta/\Delta}$ mice, which showed a lengthened circadian period (Vitaterna et al. 1994), $Npas2^{-/-}$ mice (Garcia et al. 2000) have a shorter period of activity (Dudley et al. 2003) whereas $Clock^{-/-}/Npas2^{-/-}$ double KO are completely arrhythmic (DeBruyne et al. 2007). This suggested that CLOCK and NPAS2 function as redundant regulators of circadian behavior. With regard to sleep, $Npas2^{-/-}$ mice were found to sleep less in the latter half of the baseline dark period, a time of day at which sleep need is high and WT mice showed a consolidated period of sleep (i.e., a nap) conceivably to discharge accumulated sleep pressure (Franken et al. 2006). After SD, these mice were incapable in initiating the appropriate compensatory behavior during the circadian phase in which mice are usually awake, i.e., the dark period (Franken et al. 2006). They regained less NREM sleep in the following hours after SD, and the EEG delta power after SD was smaller. Based on simulation analysis, the estimated rate at which EEG delta power increases during wakefulness tended to be slower in $Npas2^{-/-}$ mice. In conclusion, NPAS2 affects the homeostatic regulation of NREM sleep and, in contrast to $Clock^{\Delta/\Delta}$ mice, homeostatic regulation of REM sleep was not affected.

Mice lacking both *Cry1* and *Cry2* genes lack a functioning circadian clock and are behaviorally arrhythmic when kept under constant conditions (van der Horst et al. 1999; Vitaterna et al. 1999). Under baseline light–dark conditions, $Cry1,2^{-/-}$ mice spent more time in NREM sleep and sleep was more consolidated (i.e., longer uninterrupted episodes of NREM sleep). This increased consolidation of sleep was accompanied by a higher level of EEG delta power. In contrast to $Npas2^{-/-}$ mice, simulation analysis revealed that these higher levels of EEG delta power were due to a faster rate at which EEG delta power increases during wakefulness in $Cry1,2^{-/-}$ mice, compared to control mice (Wisor et al. 2002). The apparent higher sleep drive during baseline could also explain that after SD, $Cry1,2^{-/-}$ mice did not exhibit significant increases in NREM and REM sleep time, and only a brief and smaller increase in EEG delta power. These results were not observed in the $Cry1^{-/-}$ and $Cry2^{-/-}$ single KO mice (Wisor et al. 2008), consistent with the functional redundancy between the two CRY proteins observed for circadian rhythms (van der Horst et al. 1999; Vitaterna et al. 1999).

Albumin D-binding protein (DBP) is a PAR leucine zipper transcription factor that is expressed according to a robust circadian rhythm in the SCN. Mice lacking DBP display a shorter circadian period in locomotor activity and are less active (Lopez-Molina et al. 1997). Although DBP is not essential for circadian rhythm generation, it does modulate the expression of core clock components as well as

important clock outputs (Bozek et al. 2009). In particular, in vitro and in vivo studies have shown that the expression of the *Per* and *Cry1* genes is modulated through activation of the D-box in their promoter, an element that is bound by DBP (Vatine et al. 2009; Yamajuku et al. 2010, 2011; Ukai-Tadenuma et al. 2011; Mracek et al. 2012). Mice lacking the *Dbp* gene showed an altered sleep–wake distribution in baseline with reduced amplitude of the daily changes (Franken et al. 2000). These findings suggest that DBP, in addition to changing the period of the circadian clock, modifies the strength of the SCN output signal, which governs the distribution and consolidation of sleep and wakefulness over the day (Dijk and Czeisler 1995). In addition, $Dbp^{-/-}$ mice showed a decreased NREM sleep consolidation and EEG delta power amplitude, suggesting an overall lower sleep propensity. Computer simulations predicting the time course of EEG delta power demonstrated that the difference in EEG delta power was, to a large extent, due to a reduction in the circadian amplitude of the distribution of sleep and wakefulness and not to an altered dynamics of the homeostatic regulation of EEG delta power (Franken et al. 2000). This study demonstrated that DBP mostly affects those aspects of sleep that are known to be under direct circadian control but leaves the homeostatic regulation of NREM sleep unaffected. Nevertheless, similar to $Clock^{\Delta/\Delta}$ mice, $Dbp^{-/-}$ mice showed a reduced compensatory rebound in REM sleep pointing to an altered homeostatic regulation of REM sleep.

Per1 and *Per2* represent key element of the mammalian molecular clock in the SCN, and their disruption leads to gradual loss of rhythmicity under constant conditions. Two studies have investigated a possible role of *Per* genes in sleep homeostasis using mutant lines. In a first study, Kopp and colleagues observed that the main differences between genotypes occurred in the distribution of sleep and wakefulness over the day under baseline conditions (Kopp et al. 2002). *Per1* mutants slept less than WT in the dark period, whereas *Per2* mutants slept less before dark onset. This earlier decrease of sleep in *Per2* mutants is consistent with the earlier onset of the active phase in these mice. Although the authors concluded that both *Per1* and *Per2* mutants mice had intact sleep homeostasis, SD led to a larger increase in total sleep time during recovery in *Per2* mutants. Moreover, both mutant lines showed earlier onset of NREM and REM sleep rebound after the SD and *Per2* mutant mice showed a larger relative increase in sleep time in the recovery dark period. Finally, lower levels of EEG delta power were reached during recovery sleep immediately following the SD. Together these observations would argue for altered dynamics of the sleep homeostat. In a second study, Shiromani and colleagues recorded sleep in *Per1*, *Per2,* and *Per1,2* double mutant animals (Shiromani et al. 2004). Similar to the previous findings, they observed an altered sleep–wake distribution especially in *Per2* mutant and double mutant mice. More importantly, the authors observed that after 6 h SD, the rebound in EEG delta power was longer lasting in *Per1* and *Per1,2* mutant mice. Although the authors did not comment on the differences in the magnitude of the response, the relative increase in EEG delta power after SD seemed also larger in *Per1* and *Per1, 2* mutant mice. Thus in contrast to the authors' conclusion these clock genes do seem to alter the dynamics of the sleep homeostatic process albeit the genotype

effects on the increase in EEG delta power seem opposite to those reported by Kopp et al. (Kopp et al. 2002). Also *Drosophila Per* mutant flies exhibit a homeostatic phenotype, with an increased sleep rebound compared to WT flies (Shaw et al. 2002). Together, these data support a role for *Per1* and *Per2* signaling in sleep homeostasis although results in mice deserve further investigation.

While, *Per1* and *Per2* are widely considered to be integral part of the core circadian clock machinery, the role of the third *Per* homologue, *Per3*, in maintaining circadian rhythmicity is controversial. This controversy comes from observations that in mice, the absence of *Per3* has only a subtle effect on circadian rhythm phenotype (Shearman et al. 2000; reviewed in van der Veen and Archer 2010). Disruption of *Per3* in mice seems to alter (non-circadian) light-sensitivity which in turn could result in some of the circadian phenotypes reported such as a shortening of the free-running period under constant dark conditions (Van der Veen and Archer 2010). In the aforementioned study Shiromani and colleagues also recorded sleep in *Per3* mutant mice but did not note any differences in the increase of time spent asleep or EEG delta power during recovery from SD (Shiromani et al. 2004). However, in a more recent paper homeostatic sleep phenotypes were reported for $Per3^{-/-}$ mice (Hasan et al. 2011). Differences in the rebound in REM sleep were found during recovery from SD. These differences must, however, be attributed to baseline differences at the time the SD was performed because the recovery dynamics in REM sleep time as well as the levels reached in recovery did not differ. The resulting gain–loss curve resembles the hypothetical example presented in Fig. 2b′. Also the levels of EEG delta power reached after SD did not differ between $Per3^{-/-}$ and wild-type mice suggesting that the rate of increase of homeostatic sleep pressure during the SD was similar. Nevertheless, EEG delta power during the dark periods of baseline and recovery was significantly higher in $Per3^{-/-}$ mice, a difference that could not be explained by alterations in the amount or distribution of EEG delta power between the two genotypes. Thus like its role in circadian rhythms, a critical role for *Per3* in the homeostatic regulation of sleep in the mouse remains questionable.

In humans, a primate-specific variable number tandem repeat (VNTR) polymorphism in the *Per3* gene was investigated a few years ago for its role in circadian rhythmicity (Jenkins et al. 2005). A 54-nucleotide coding-region segment of the gene is repeated either 4 or 5 times, leading to different alleles. Initially, an association study revealed a higher frequency of people homozygous for the 5-repeat in morning types than in evening types suggesting possible functional role for *Per3* in sleep and circadian behavior (Archer et al. 2003). In follow-up studies investigating sleep phenotypes in *Per3* 4/4 and 5/5 carriers, it was found that this polymorphism affected electrophysiological and behavioral markers of sleep homeostasis such as sleep latency, EEG delta power, and the decrement in waking performance (Viola et al. 2007, 2012), executive function (Groeger et al. 2008), and neurobehavioral performance after sleep restriction (Rupp et al. 2012). This was the first evidence in human of a non-circadian role of clock genes in sleep regulation (Dijk and Archer 2009). While the human *Per3* VNTR polymorphism has been linked with differences in sleep homeostasis,

cognitive vulnerability to sleep loss, and differences in functional MRI-assessed brain activity in response to sleep loss (Dijk and Archer 2009), none of these studies has shown any association between the *Per3* VNTR and any circadian phenotype. Thus, while other core clock proteins may have overlapping roles in both the circadian and sleep systems, PER3 phenotypes from human and animal studies point toward a more prominent role for PER3 in the regulation of sleep homeostasis. A new transgenic mouse line carrying the human *Per3* polymorphism in the mouse *Per3* gene is currently under investigation, and preliminary analyses seem to highlight similarities with the human sleep homeostatic phenotype (Hasan et al. 2012).

DEC2, a member of the basic helix-loop protein family of transcription factors, by repressing CLOCK::BMAL1 acts as a negative component of the circadian clock. In a family-based candidate gene resequencing study a point mutation in the *Dec2* gene (P385R) was found to be associated with extremely early wake-up times and reduced sleep time (He et al. 2009). To examine the effect of DEC2 on sleep, several animal models were constructed. In transgenic mice carrying the human P385R *Dec2* gene, both NREM sleep and REM sleep were reduced and sleep was more fragmented in baseline compared to mice carrying the wild-type human *Dec2* thus recapitulating the human short sleep phenotype. A 6 h SD in P385R *Dec2* mice resulted in a smaller rebound in both NREM sleep and REM sleep, and a smaller relative increase in EEG delta power, compared to the control mice. The loss–gain analyses of the effect of SD on REM sleep duration revealed, however, a dynamics resembling our example depicted in Fig. 2b, indicating that the apparent difference in REM sleep homeostasis might be due to differences to REM sleep in baseline. Also the analyses of the rebound in EEG delta power do not allow for a careful evaluation of genotype differences in the sleep–wake dependent dynamics; given the poor time resolution over which EEG delta power was calculated (6 h intervals), it is impossible to establish whether the reported smaller increase after SD is due a slower build-up of sleep need during the SD, a faster decrease of sleep need during recovery sleep, or to differences in NREM sleep during the initial 6 h of recovery sleep. In both P385R *Dec2* transgenic mice and in *Dec2* KO mice the compensation of NREM sleep duration lost during the 6 h SD was compromised pointing to a role of *Dec2* in this aspect of sleep homeostasis specifically. In line with the human and mouse short sleep phenotype, transgenic flies expressing the murine *Dec2* gene carrying the human mutation P385R slept less than control flies (He et al. 2009). Unfortunately, the response to a homeostatic challenge (i.e., SD) was not assessed in these flies nor in humans. Although more data are needed, these data suggest that the P385R genotype shortens sleep independent of species background.

5.2 Clock Gene Expression Changes as a Function of Sleep

In line with the findings that several clock genes are involved in the control of sleep homeostasis, several studies have shown that expression of some clock genes in the mouse brain varies as a function of sleep propensity. SD results in a constellation of changes in gene expression in the brain (Cirelli et al. 2006; Terao et al. 2006; Maret et al. 2007; Thompson et al. 2010) that are sleep–wake related and thus, can serve as biomarkers for sleep loss and recovery (see Sect. 8). Among the transcripts that exhibit sleep-related changes in the cortex are the circadian genes *Per1*, *Per2,* and *Dbp* (Wisor et al. 2002; Franken et al. 2006, 2007; Mongrain 2010; Curie et al. 2013). The expression of *Per1* and *Per2* increases according to a linear function of the duration of the time mice are kept awake, whereas the expression of *Dbp* decreases (Wisor et al. 2002; Franken et al. 2006, 2007). These SD-induced changes were, however, strongly dependent on the time of day at which the SD was performed (Curie et al. 2013). Moreover, the SD-associated increase in corticosterone proved to be an important contributor to these increase in clock gene expression such that the expression of *Per1* did no longer increase after SD in adrenalectomized mice (Mongrain et al. 2010). In addition to stress, SD seems to be able to alter the clock gene expression through directly modifying DNA-binding of the transcription factors CLOCK, BMAL1, and NPAS2 to specific E-boxes in clock gene promoters (Mongrain et al. 2011).

Together, the data from human, mice, and flies have contributed to the notion that, at the molecular level, sleep homeostasis and circadian rhythms are not independent, and that clock genes participate in both aspects of sleep regulation. According to the fact that several clock genes belong to a class of PAS transcriptional regulators that can act as sensors of environmental signals (Gu et al. 2000), we proposed that clock genes and their protein products act as molecular sensors and translate homeostatic sleep need into transcriptional signals at the cellular level, independent of the circadian machinery (Franken and Dijk 2009). Especially, the sensitivity of the clock gene machinery to redox state and metabolism (Bass and Takahashi 2010) is of interest in the context of sleep homeostasis as maintaining metabolic balance is often mentioned as a potential key function of sleep.

6 Genes of the Adenosine Pathway as Homeostatic Regulators?

Adenosine is an inhibitory neuromodulator that has been proposed to act as a homeostatic regulator of sleep and to link humoral and neural mechanisms of sleep–wake regulation (Porkka-Heiskanen et al. 1997, 2000; Basheer et al. 2004; Kalinchuk et al. 2011). In mammals, four subtypes of G-protein coupled receptors mediate the effects of adenosine: A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R and two of them have been investigated for their role in sleep homeostasis (Fredholm et al. 2001).

It is thought that A_1R are responsible of the sleep effects of adenosine (Rainnie et al. 1994; Benington and Heller 1995), but a careful study performed in A_1R KO mice showed that the homeostatic aspect of sleep regulation was unaltered in animals lacking A_1R (Stenberg et al. 2003). This study revealed that mice lacking A_1R had normal baseline sleep–wake distribution and responded normally to sleep pressure, with NREM sleep rebound and EEG delta power rebound being similar to WT animals. More recently, a conditional central nervous system KO of this adenosine receptor was created. $A1R^{-/-}$ mice were found to have reduced EEG delta power in NREM sleep during baseline, as well as during sleep restriction (Bjorness et al. 2009) whereas the sleep–wake distribution and amount were preserved. More importantly, when the mice were allowed to sleep for 2 h following 4 h of sleep restriction, the relative increase in EEG delta power during NREM sleep above baseline levels was smaller in the KO mice although the amount of time spent in NREM sleep was similar to WT. The authors suggested that the elevated sleep need signaled by adenosine is, at least in part, mediated through the A_1R. However, the implemented sleep restriction protocol allows mice to recover during the 2 h sleep opportunity windows between the 4 h SDs, importantly affecting the level of EEG delta power. Moreover, the authors observed a general decrease in EEG delta power when calculated over all states (wakefulness, NREM and REM sleep) which might indicate a specific effect of the gene on general electrical brain activity rather than an effect on sleep homeostasis. Given the contradictory findings, the role of A_1R in sleep homeostasis remains unclear. It might be interesting to generate inducible KO animals to study the loss of A_1R in the adult stage only, thereby circumventing several potential confounds such as developmental compensation. The accumulated evidence indicates that besides A_1R also $A_{2A}R$ contributes to the effects of adenosine on sleep. A preliminary report indicated that $A_{2A}R$ KO mice do not show a NREM sleep rebound following 6 h SD, revealing an altered sleep homeostasis in these mice (Urade et al. 2003). Changes in EEG delta power were not reported in these mice. Along the same line, a human study revealed that a distinct polymorphism in the gene encoding the $A_{2A}R$, *Adora2*, modulates individual sensitivity to subjective and objective effects of caffeine on sleep (Rétey et al. 2007). It would be of interest to test the effect of this polymorphism on the homeostatic process by submitting individuals carrying the different polymorphism to a SD. In *Drosophila*, one single adenosine receptor gene has been identified, *dAdoR*, that is most closely related to the mammalian *Adora2* gene. Study in *dAdoR* mutant flies revealed that sleep was not affected by the mutation, neither in baseline, nor in recovery from SD (Wu et al. 2009). These results suggest that in flies, adenosine receptors are not required to maintain sleep homeostasis.

Besides the receptors, adenosine metabolism has also been investigated in the context of sleep homeostasis. Intracellular adenosine levels are regulated by enzymes such as adenosine kinase (ADK) and adenosine deaminase. ADK is the key enzyme controlling adenosine levels, and the effect of its overexpression on sleep has been investigated in mice (Palchykova et al. 2010). ADK transgenic mice (*Adk-tg*), which have an increased enzyme activity, are thought to have lower adenosine tone in the brain (Fedele et al. 2005). In *Adk-tg* mice, sleep–wake

baseline distribution is altered, the mice being more active and sleeping less than the WT controls, especially during the dark period. After 6 h SD, these mice compensated with a lower EEG delta power in NREM sleep than the WT, despite a larger NREM sleep rebound. The authors suggested that *Adk-tg* mice have a reduced capacity to intensify sleep, and that adenosine metabolism plays an important role in maintaining sleep homeostasis. However, the increased amount of NREM sleep obtained during recovery sleep in *Adk-tg* mice could underlie the lower EEG delta power levels reached. In addition, the recovery time course of EEG delta power of *Adk-tg* and WT mice ran largerly in parallel which might point a problem with the choice of the baseline reference chosen to normalize the individual data. As outlined in Sect. 4, the baseline amount and distribution of NREM sleep can affect the level of the reference when the 24 h average EEG delta power is used. *Adk-tg* mice have less NREM sleep in the baseline period which can be expected to be accompanied to higher levels of EEG delta power in baseline and thus a higher reference value and to reduced relative levels during recovery. Unfortunately, the authors did not show the baseline time course of EEG delta power to counter this concern. Several other enzymes are involved in the conversion of adenosine nucleotides to adenosine. Extracellular AMP is converted into adenosine by the 5′ectonucleotidase enzyme CD73. A recent study of mice lacking CD73, that are thought to have a reduced capacity to enhance extracellular adenosine levels, has shown that CD73 KO mice have more spontaneous NREM sleep time, although less consolidated (Zielinski et al. 2012). After 6 h of enforced waking, KO mice had a smaller NREM sleep rebound and a smaller increase in EEG delta power over baseline levels, compared to WT. However, the time course of EEG delta power in recovery sleep is very similar in WT and KO mice and the relative differences between genotypes reported after SD have to be attributed to differences in the baseline time course of EEG delta power, suggesting that the homeostatic response is unaltered.

An important general concern of the KO studies dealing with adenosine signaling is the lack of information about the adenosine levels in the brain. In vivo measurement of extracellular adenosine levels is critical and controversial, because of difficulties in performing correct local adenosine measurement in brain tissue and because of large variations according to the methods used (Delaney and Geiger 1996; Latini and Pedata 2001). Thus, many studies are based on the assumption that adenosine levels are altered by the genetic manipulation in the synthesis/metabolism pathway. Some authors did make use of indirect measure of adenosine levels, by evaluating the activity of adenosine receptors using electrophysiology, without direct evidence that adenosine levels are effectively altered in the mice (Fedele et al. 2005). Therefore, it should be kept in mind that the phenotypes observed are not necessarily directly linked to an alteration of adenosine levels, and could be due to other deficits resulting from the genetic manipulation of the pathway.

Besides the receptors and metabolic pathway described above, other components seem to act in concert with adenosine in modulating sleep homeostasis. Prostaglandin 2, thought to be one of the most powerful sleep-promoting substances (Urade and Hayaishi 2011 for review), modulates adenosine levels in the

brain (Mizoguchi et al. 2001), and is believed to be indirectly involved in sleep homeostasis through its receptors and producing enzymes (Mizoguchi et al. 2001; Hayaishi et al. 2004). However, it remains unknown if the role of Prostaglandin 2 in sleep regulation can be dissociated from the adenosine signaling pathway, but it seems clear that these two molecules contribute to the sleep-wake control and probably to sleep homeostasis (Huang et al. 2007 for review).

Moreover, recent studies have highlighted a role for glial cells, and in particular astrocytes, in modulating the accumulation of sleep pressure through a pathway involving adenosine receptors (Halassa et al. 2009; Schmitt et al. 2012). Together, these data strongly suggest an involvement of adenosine and the associated pathways in the modulation of sleep homeostasis.

7 Other Signaling Pathways and Sleep Homeostasis

Under this section, we present only some examples of the signaling pathways in the brain that have been studied in the context of sleep homeostasis using forward and reverse genetic techniques.

7.1 Neurotransmitters

Many neurotransmission systems have been involved in the control of sleep and wakefulness, revealing that the neurobiology of sleep relies on the interaction of wake and sleep-promoting centers in the brain (Brown et al. 2012 for review). Among these systems, some of them have been shown to impact the homeostatic control of sleep as well. In flies, genetic manipulation of the dopamine system was found to impact on sleep homeostasis (Andretic et al. 2005; Kume et al. 2005; Wu et al. 2008; Qu et al. 2010); similar results were obtained with genes involved in monoamine catabolism (Shaw et al. 2000). In the mouse, several studies have suggested a role for serotonin in the control of sleep homeostasis (Frank et al. 2002; Popa et al. 2006). Along the same lines, human polymorphism in the *Catechol-O-methyltransferase* gene, which encodes for the principal enzyme involved in catecholamine's degradation, has been linked to EEG differences during sleep loss and differential homeostatic response to SD (Bodenmann et al. 2009; Goel et al. 2011). Together, these data from flies, mice and humans suggest a role for catecholamine system in sleep homeostasis in addition to its well established role in sleep-wake regulation.

Besides the previously mentioned wake-promoting molecules, the inhibitory neurotransmitter GABA has also been investigated for its role in sleep homeostasis. In mice, several reverse genetic studies have investigated the contribution of the GABA receptors in sleep homeostasis but it appeared that this major component of the sleep–wake gating control does not play a major role in sleep homeostasis (Winsky-Sommerer et al. 2009; Vienne et al. 2010).

In summary, although the role for neurotransmitters in sleep–wake regulation has largely been demonstrated in mammalian and non-mammalian species, their involvement in sleep homeostasis is less obvious. This strongly supports the notion that the maintenance of a proper homeostatic sleep balance involves other factors than those implied in the regulation of the behavioral states alternation and requires independent mechanisms.

7.2 Ion Channels

In both mammals and flies, potassium currents play a major role in the control of membrane excitability and transmitter release. One of the first large-scale forward screens in *Drosophila* has highlighted the function of the voltage-gated potassium channel Shaker (*Sh*) in sleep (Cirelli et al. 2005). Subsequent mutagenesis screens identified mutants in the SH potassium channel and a novel SH regulator, called Sleepless (SSS), that exhibit dramatically reduced sleep amounts, losing as much as 80 % of total sleep in a *sss* mutant (Koh et al. 2008). In addition, mutants of an SH regulatory subunit, Hyperkinetic (*Hk*) also show a reduction in sleep time (Bushey et al. 2007). These mutagenesis studies in the fly highlighted the central role of membrane excitability and subsequent control of neurotransmitter release in sleep regulation, in particular in the homeostatic aspect of sleep. In mice, a mutation in *Kcna2*, the closest homolog to *Drosophila Sh,* produces a reduction in sleep amount (Douglas et al. 2007). The response to SD could, however, not be assessed in these mice because of seizures and premature death. Together, the fly and mouse studies are indicative of the importance of ion channels, and in particular potassium channels, in the control of sleep and its EEG correlates.

7.3 Cytokines and Neurotrophic Factors

Cytokines represent another group of signaling molecules that have been linked to sleep and its homeostatic regulation. One particular cytokine, Tumor Necrosis Factor alpha (TNFα) is considered as a sleep-promoting factor and was found to affect sleep homeostasis (Clinton et al. 2011; Krueger et al. 2011 for review). In human, plasma TNFα levels are correlated with EEG delta power (Darko et al. 1995), and manipulating TNFα concentration in animals result in changes in NREM sleep time and EEG delta power levels (Yoshida et al. 2004; Taishi et al. 2007). Several transgenic mouse lines carrying targeted mutations of the TNFα signaling pathway have been investigated for a sleep phenotype (for review, see Krueger 2008). For example, mice lacking the TNF 55 kDa receptor fail to increase the amount of NREM sleep in response to TNFα treatment (Fang et al. 1997). Another study showed that the deficiency of one or two of the TNF receptors, or the deficiency of the ligand to the receptors reduces the amount of REM sleep and increases

EEG delta power after 6 h SD. In receptor 2 and ligand KO, the increase in EEG delta power concerned the faster delta frequencies (2.75–4.0 Hz) whereas in receptor 1 KO this increase was limited to the slower frequencies (0.75–2.5 Hz) (Deboer et al. 2002). More recently, the TNFα receptor double KO mice were investigated for a sleep homeostatic phenotype and showed shorter sleep latency and an altered rebound in both NREM sleep and REM sleep after a sleep fragmentation protocol (Kaushal et al. 2012). In sum, these data support a role for this cytokine in sleep homeostasis.

Brain-derived neurotrophic factor (BDNF) has been proposed to regulate sleep need in several models. Studies in the rat provided evidence for a causal role of BDNF secretion in sleep homeostasis (Huber et al. 2007; Faraguna et al. 2008). In humans, one functional polymorphism has been found in the gene encoding for the BNDF located on chromosome 11 (Egan et al. 2003). A recent study evaluated the effect of this polymorphism on sleep intensity and found a difference in NREM sleep amount and EEG delta power in both baseline and recovery from 40 h of SD (Bachmann et al. 2012). To better understand whether BDNF plays a causal role in regulating sleep homeostasis it might be interesting to evaluate sleep and response to SD in BDNF KO animals.

Converging observations pointed out a bidirectional interaction between sleep and the endocrine system; many hormonal secretions are correlated to sleep-wake distribution, and the secretion of several hormones is modified during extended wakefulness and recovery sleep (Takahashi et al. 1968, 1981; for review see Obal and Krueger 2004). Several KO studies in mice have investigated the involvement of the somatotropic axis, and in particular growth hormone in modulating sleep need (Obal et al. 2001, 2003; Hajdu et al. 2002). In conclusion of these studies, whereas the role of the somatotropic axis in sleep promoting is established, its involvement in the homeostatic control of sleep seems less evident.

Another growth factor pathway that has been discovered to affect sleep is the one involving epidermal growth factor receptor (EGFR). When the EGFR ligands Rho or Star are induced in flies, they lead to an increase sleep level and sleep consolidation (Foltenyi et al. 2007). More importantly, modulation of EGFR signaling in flies affects not only sleep amounts, but also recovery sleep. In mammals, the functional consequences of EGFR/ERK activation on sleep are unknown; however, a report from sleep deprived rats suggests a link between ERK activation, sleep and memory (Guan et al. 2004).

8 Molecular Changes Associated to Sleep Loss: Insights from Molecular Genetics Studies

As mentioned earlier, molecular genetic methods led to the discovery that SD results in a variety of changes in gene expression in the brain. Using microarray analysis, studies performed in rats, mice, and flies showed that several classes of

genes are up- or down-regulated after spontaneous waking or during SD relative to sleep. These classes include immediate early genes and transcription factors, genes related to energy metabolism, growth factors and adhesion molecules, chaperones and heat shock proteins, vesicle- and synapse-related genes, neurotransmitters, transporters and hormone receptors, and different types of enzymes (Cirelli and Tononi 2000; Cirelli 2005; Terao et al. 2006; Mackiewicz et al. 2007; Maret et al. 2007). Interestingly, among the many transcripts that change following SD, a class of small non-coding RNA molecules, the micro-RNAs, was discovered in microarray screens (Davis et al. 2007; Mongrain et al. 2010).

More recently, the microarray-based profiling methods have been used in conjunction with immediate early genes-based activity-mapping or high-throughput in situ hybridization (Terao et al. 2006; Lein et al. 2007; Thompson et al. 2010) to determine changes in specific brain regions that are associated to extended wakefulness and therefore provide an anatomical map of the SD effects.

Although transcriptome studies offer a first insight into the changes associated with sleep loss, the challenge remains to find genes, or classes of genes, that are causally linked to sleep need, and distinguish them from transcripts that change due to secondary effects of sleep loss or to the SD method. An example of such an effect is the surge in corticosterone associated with SD. By comparing the SD-induced changes in brain gene expression between sham-operated and adrenalectomized mice in which corticosterone levels do not change when sleep deprived it was found that corticosterone importantly amplifies the SD induced changes (Mongrain et al. 2010). By combining these results with the changes in gene expression after spontaneous sustained periods of wakefulness during baseline, genes could be selected for which the expression was affected mostly by increased sleep need. The resulting exclusive list of 78 might be regarded as candidate molecular components of the sleep homeostat as exemplified by the transcript *Homer1a* (see next section below) present on this list (Mongrain et al. 2010).

To add causality, transcriptome studies can be complemented with reverse genetic studies. As an example of the involvement of heat shock protein in sleep homeostasis, mutant flies for heat shock proteins showed an altered homeostatic response to sleep loss, whereas heat shocking flies before SD rescues the premature lethality that is due to SD in *Cycle* mutant flies (Shaw et al. 2002). A similar example is provided by the immunoglobulin binding protein, indicative of stress, which is increased in the mouse cerebral cortex as well as in *Drosophila* heads in response to sleep loss (Cirelli and Tonini 2000; Shaw et al. 2000; Mackiewicz et al. 2003; Naidoo et al. 2005). In flies overexpressing immunoglobulin binding protein, the response to SD is altered compared to the control line (Naidoo et al. 2007). These studies provide good examples of a combination of several genetic techniques to uncover the genetics of sleep homeostasis.

8.1 *The Identification of* Homer1a *as a Molecular Correlate of Sleep Loss*

Homer proteins constitute a family of scaffolding proteins localized in the post-synaptic density of excitatory synapses that function as molecular adaptators by binding to specific prolin-rich sequence in the C-terminus of metabotropic glutamate receptors and other proteins that play a role in calcium signaling. The vertebrate genome includes three *Homer* genes (*Homer1, -2,* and *-3*). *Homer1* is a complex gene with multiple splice variants among which: *Homer1a*, *-b,* and *-c*. Interest in *Homer1a* comes from its role in homeostatic synaptic scaling (Hu et al. 2010) and neuroprotection (Szumlinski et al. 2006) both suggested as possible functions of sleep (Tononi and Cirelli 2006; Mongrain et al. 2010). *Homer1a* is a short form that is up-regulated with neuronal activity and antagonizes the activity of the full length HOMER1b and -c proteins by competing for binding to the glutamate receptors. In contrast, *Drosophila* possesses a single *Homer* gene that encodes a cross-linking HOMER protein but no *Homer1a* homologue. In a study that involved in-depth phenotyping of sleep in recombinant inbred mice, a QTL for sleep homeostasis was identified (Franken et al. 2001). A genome-wide significant QTL for the increase of EEG delta power after SD was identified on chromosome 13, referred to as delta power in slow-wave sleep 1 (*Dps1*). This QTL accounted for 49 % of the variance in this trait between C57BL/6 J and DBA/2 J strains. Further in silico and transcriptome analyses using microarrays identified *Homer1a* as a potentially credible candidate gene for *Dps1* (Maret et al. 2007). A parallel study confirmed this finding by identifying genes that were both located in the *Dps1* region and differentially expressed between sleep and wakefulness in the brain of C57BL/6 J mice (Mackiewicz et al. 2008). These findings were concordant with previous expression analyses in flies showing that *Homer* expression is changed during sleep and extended wakefulness in flies (Zimmerman et al. 2006). However, it remained unknown whether changes in expression play a causal role in sleep-wake control or are simply a correlate of these behavioral states. A careful study recently investigated sleep and its homeostatic regulation in mutant animals for the *Homer* genes, and showed that these proteins play a role in sustaining sleep-wake behavioral states in both *Drosophila* and mice (Naidoo et al. 2012). In *Drosophila*, lack of *Homer* leads to an alteration in the ability to sustain both sleep and wakefulness but the effect on sleep consolidation is greater; moreover, the *Homer* null flies have an altered response to SD with a longer recovery period, although less consolidated, suggesting that the recovery period does not efficiently dissipate the drive for sleep. In contrast, in mice the major effect of *Homer1a* absence is their inability to sustain long bouts of wakefulness. Interest in *Homer1* was based primarily on it being a candidate for *Dps1* QTL for the rebound in EEG delta power after SD. No altered response to SD was, however, observed for the increase in EEG delta power in these *Homer1a* KO mice confirming the lack of a homeostatic phenotype in total *Homer1* (i.e., *Homer1a*, *-b*, and *-c*) KO mice (Maret et al. 2007). The authors concluded that HOMER1 scaffolding proteins are required for maintenance of behavioral state and that

consolidation of sleep and wake is governed by molecules other than traditionally known neurotransmitters. They also noted that in a model of competitive actions of *Homer1a* versus cross-linking forms of *Homer*, the up-regulation of *Homer1a* is functionally equivalent to down-regulation of cross-linking *Homer*. Thus, despite evolutionary changes in *Homer* gene structure and copy number, *Drosophila* and mice share the functional consequence of reduced *Homer* cross-linking during wakefulness and increased during sleep. Although the causal role of *Homer1a* in the control of sleep homeostasis remains unclear, it is to date the best know molecular marker of sleep need. Further studies using inducible KO in the adult animal will probably help to by-pass issues such as developmental compensation. The *Homer1a* discovery is one of the few examples of a successful combination of forward, molecular, and reverse genetic approaches.

9 Conclusion

Sleep homeostasis is a complex mechanism of control, and defining an alteration in this process as a genetic trait is obviously not simple or straightforward. In this review, we discussed the variables and parameters used to evaluate sleep homeostasis in animal models. Because different studies focus on different aspects of sleep homeostasis using different methods and analyses, comparisons among studies are difficult. In search for the molecular basis of sleep homeostasis, several genetic methods have been applied, and the combination of forward, reverse, and molecular genetic approaches across species offered promising results. Within the past few years, the development of microarray technologies has enabled to study the expression of genes that are changed with SD, and could highlight many pathways and molecules that are linked to sleep homeostasis such as the molecular circadian clock, metabolism, synaptic plasticity, immune response, and others. With the use of transgenic animals, researchers have tried to reveal causal relationship between these candidate genes and homeostatic process. However, controversial results in the various animal models confirm that sleep homeostasis is indeed complex and that many different pathways are likely to be involved. Here we have tried to give a critical overview of candidate genes that have been tested as regulator of sleep homeostasis, but the list is not exhaustive. Moreover, although not mentioned in our review, sleep homeostasis has been found to differ between males and females in some species, which suggests the possible involvement of other pathways related to hormones. In the future, the use of a combination of system genetic approaches in the mouse or other animal models, and GWAS in humans will probably be our best bet to uncover the molecular actors central to sleep homeostasis.

References

Achermann P, Borbely AA (2003) Mathematical models of sleep regulation. Front Biosci 8:s683–s693

Aeschbach D, Cajochen C, Landolt H, Borbely AA (1996) Homeostatic sleep regulation in habitual short sleepers and long sleepers. Am J Physiol 270:R41–R53

Aeschbach D, Matthews JR, Postolache TT, Jackson MA, Giesen HA, Wehr TA (1997) Dynamics of the human EEG during prolonged wakefulness: evidence for frequency-specific circadian and homeostatic influences. Neurosci Lett 239:121–124

Aeschbach D, Postolache TT, Sher L, Matthews JR, Jackson MA, Wehr TA (2001) Evidence from the waking electroencephalogram that short sleepers live under higher homeostatic sleep pressure than long sleepers. Neuroscience 102:493–502

Altshuler D, Daly MJ, Lander ES (2008) Genetic mapping in human disease. Science 322:881–888

Ambrosius U, Lietzenmaier S, Wehrle R, Wichniak A, Kalus S, Winkelmann J, Bettecken T, Holsboer F, Yassouridis A, Friess E (2008) Heritability of sleep electroencephalogram. Biol Psychiatry 64:344–348

Amici R, Cerri M, Ocampo-Garces A, Baracchi F, Dentico D, Jones CA, Luppi M, Perez E, Parmeggiani PL, Zamboni G (2008) Cold exposure and sleep in the rat: REM sleep homeostasis and body size. Sleep 31:708–715

Andretic R, Franken P, Tafti M (2008) Genetics of sleep. Annu Rev Genet 42:361–388

Andretic R, van Swinderen B, Greenspan RJ (2005) Dopaminergic modulation of arousal in Drosophila. Curr Biol 15(13):1165–1175

Antoch MP, Song EJ, Chang AM, Vitaterna MH, Zhao Y, Wilsbacher LD, Sangoram AM, King DP, Pinto LH, Takahashi JS (1997) Functional identification of the mouse circadian Clock gene by transgenic BAC rescue. Cell 89:655–667

Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, von Schantz M (2003) A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep 26:413–415

Ayroles JF, Carbone MA, Stone EA, Jordan KW, Lyman RF, Magwire MM, Rollmann SM, Duncan LH, Lawrence F, Anholt RR, Mackay TF (2009) Systems genetics of complex traits in Drosophila melanogaster. Nat Genet 41:299–307

Bachmann V, Klein C, Bodenmann S, Schafer N, Berger W, Brugger P, Landolt HP (2012) The BDNF Val66Met polymorphism modulates sleep intensity: EEG frequency- and state-specificity. Sleep 35:335–344

Basheer R, Strecker RE, Thakkar MM, McCarley RW (2004) Adenosine and sleep-wake regulation. Prog Neurobiol 73:379–396

Bass J, Takahashi JS (2010) Circadian integration of metabolism and energetics. Science 330:1349–1354

Belknap JK, Hitzemann R, Crabbe JC, Phillips TJ, Buck KJ, Williams RW (2001) QTL analysis and genomewide mutagenesis in mice: complementary genetic approaches to the dissection of complex traits. Behav Genet 31:5–15

Benington JH, Heller HC (1995) Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol 45:347–360

Benington JH, Woudenberg MC, Heller HC (1994) REM-sleep propensity accumulates during 2-h REM-sleep deprivation in the rest period in rats. Neurosci Lett 180:76–80

Benito J, Zheng H, Ng FS, Hardin PE (2007) Transcriptional feedback loop regulation, function, and ontogeny in Drosophila. Cold Spring Harb Symp Quant Biol 72:437–444

Bixler E (2009) Sleep and society: an epidemiological perspective. Sleep Med 10(Suppl 1):S3–S6

Bjorness TE, Kelly CL, Gao T, Poffenberger V, Greene RW (2009) Control and function of the homeostatic sleep response by adenosine A1 receptors. J Neurosci 29:1267–1276

Bodenmann S, Xu S, Luhmann UF, Arand M, Berger W, Jung HH, Landolt HP (2009) Pharmacogenetics of modafinil after sleep loss: catechol-O-methyltransferase genotype modulates waking functions but not recovery sleep. Clin Pharmacol Ther 85:296–304

Borbely AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195–204

Borbely AA, Achermann P (1991) Ultradian dynamics of sleep after a single dose of benzodiazepine hypnotics. Eur J Pharmacol 195:11–18

Borbély AA, Tobler I, Hanagasioglu M (1984) Effect of sleep deprivation on sleep and EEG power spectra in the rat. Behav Brain Res 14(3):171–182

Bozek K, Relogio A, Kielbasa SM, Heine M, Dame C, Kramer A, Herzel H (2009) Regulation of clock-controlled genes in mammals. PLoS ONE 4:e4882

Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW (2012) Control of sleep and wakefulness. Physiol Rev 92:1087–1187

Bushey D, Huber R, Tononi G, Cirelli C (2007) Drosophila Hyperkinetic mutants have reduced sleep and impaired memory. J Neurosci 27:5384–5393

Cannon WB (1915) Bodily changes in pain, hunger, fear and rage: an account of recent researches into the function of emotional excitement. Canon, New York

Chiang MC, Avedissian C, Barysheva M, Toga AW, McMahon KL, de Zubicaray GI, Wright MJ, Thompson PM (2009) Extending genetic linkage analysis to diffusion tensor images to map single gene effects on brain fiber architecture. Med Image Comput Comput Assist Interv 12:506–513

Cirelli C (2003) Searching for sleep mutants of Drosophila melanogaster. BioEssays 25:940–949

Cirelli C (2005) A molecular window on sleep: changes in gene expression between sleep and wakefulness. Neuroscientist 11:63–74

Cirelli C, Bushey D, Hill S, Huber R, Kreber R, Ganetzky B, Tononi G (2005) Reduced sleep in Drosophila Shaker mutants. Nature 434:1087–1092

Cirelli C, Faraguna U, Tononi G (2006) Changes in brain gene expression after long-term sleep deprivation. J Neurochem 98:1632–1645

Cirelli C, Gutierrez CM, Tononi G (2004) Extensive and divergent effects of sleep and wakefulness on brain gene expression. Neuron 41:35–43

Cirelli C, Tononi G (2000) Gene expression in the brain across the sleep-waking cycle. Brain Res 885:303–321

Clinton JM, Davis CJ, Zielinski MR, Jewett KA, Krueger JM (2011) Biochemical regulation of sleep and sleep biomarkers. J Clin Sleep Med 7:S38–S42

Curie T, Mongrain V, Dorsaz S, Mang GM, Emmenegger Y, Franken P (2013) Homeostatic and circadian contribution to EEG and molecular state variables of sleep regulation. Sleep 36(3):311–323

Daan S, Beersma DG, Borbely AA (1984) Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 246:R161–R183

Darko DF, Miller JC, Gallen C, White J, Koziol J, Brown SJ, Hayduk R, Atkinson JH, Assmus J, Munnell DT, Naitoh P, McCutchan JA, Mitler MM (1995) Sleep electroencephalogram delta-frequency amplitude, night plasma levels of tumor necrosis factor alpha, and human immunodeficiency virus infection. Proc Natl Acad Sci U.S.A 92:12080–12084

Darvasi A (1998) Experimental strategies for the genetic dissection of complex traits in animal models. Nat Genet 18:19–24

Davis CJ, Bohnet SG, Meyerson JM, Krueger JM (2007) Sleep loss changes microRNA levels in the brain: a possible mechanism for state-dependent translational regulation. Neurosci Lett 422:68–73

De Gennaro L, Marzano C, Fratello F, Moroni F, Pellicciari MC, Ferlazzo F, Costa S, Couyoumdjian A, Curcio G, Sforza E, Malafosse A, Finelli LA, Pasqualetti P, Ferrara M, Bertini M, Rossini PM (2008) The electroencephalographic fingerprint of sleep is genetically determined: a twin study. Ann Neurol 64:455–460

Deboer T (2009) Sleep and sleep homeostasis in constant darkness in the rat. J Sleep Res 18:357–364

Deboer T, Fontana A, Tobler I (2002) Tumor necrosis factor (TNF) ligand and TNF receptor deficiency affects sleep and the sleep EEG. J Neurophysiol 88(2):839–846
DeBruyne JP, Weaver DR, Reppert SM (2007) CLOCK and NPAS2 have overlapping roles in the suprachiasmatic circadian clock. Nat Neurosci 10:543–545
Delaney SM, Geiger JD (1996) Brain regional levels of adenosine and adenosine nucleotides in rats killed by high-energy focused microwave irradiation. J Neurosci Methods 64:151–156
Dijk DJ, Archer SN (2009) PERIOD3, circadian phenotypes, and sleep homeostasis. Sleep Med Rev 14:151–160
Dijk DJ, Beersma DG, Daan S (1987) EEG power density during nap sleep: reflection of an hourglass measuring the duration of prior wakefulness. J Biol Rhythms 2:207–219
Dijk DJ, Czeisler CA (1995) Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15:3526–3538
Dijk DJ, Franken P (2005) Interaction of sleep homeostasis and circadian rhythmicity: dependent or independent systems? In: Kryger MH, Roth T, Dement W (eds) Principles and practice of sleep medecine. Saunders/Elsevier, Philadelphia, pp 418–434
Douglas CL, Vyazovskiy V, Southard T, Chiu SY, Messing A, Tononi G, Cirelli C (2007) Sleep in Kcna2 knockout mice. BMC Biol 5:42
Dudley CA, Erbel-Sieler C, Estill SJ, Reick M, Franken P, Pitts S, McKnight SL (2003) Altered patterns of sleep and behavioral adaptability in NPAS2-deficient mice. Science 301:379–383
Easton A, Meerlo P, Bergmann B, Turek FW (2004) The suprachiasmatic nucleus regulates sleep timing and amount in mice. Sleep 27:1307–1318
Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269
Endo T, Roth C, Landolt HP, Werth E, Aeschbach D, Achermann P, Borbely AA (1998) Selective REM sleep deprivation in humans: effects on sleep and sleep EEG. Am J Physiol 274:R1186–R1194
Endo T, Schwierin B, Borbely AA, Tobler I (1997) Selective and total sleep deprivation: effect on the sleep EEG in the rat. Psychiatry Res 66:97–110
Fang J, Wang Y, Krueger JM (1997) Mice lacking the TNF 55 kDa receptor fail to sleep more after TNFalpha treatment. J Neurosci 17(15):5949–5955
Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C (2008) A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. J Neurosci 28:4088–4095
Fedele DE, Gouder N, Guttinger M, Gabernet L, Scheurer L, Rulicke T, Crestani F, Boison D (2005) Astrogliosis in epilepsy leads to overexpression of adenosine kinase, resulting in seizure aggravation. Brain 128:2383–2395
Flint J, Mott R (2001) Finding the molecular basis of quantitative traits: successes and pitfalls. Nat Rev Genet 2:437–445
Foltenyi K, Greenspan RJ, Newport JW (2007) Activation of EGFR and ERK by rhomboid signaling regulates the consolidation and maintenance of sleep in Drosophila. Nat Neurosci 10:1160–1167
Frank MG, Stryker MP, Tecott LH (2002) Sleep and sleep homeostasis in mice lacking the 5-HT2c receptor. Neuropsychopharmacology 27:869–873
Franken P (2002) Long-term vs. short-term processes regulating REM sleep. J Sleep Res 11:17–28
Franken P (2012) Genetic mechanisms underlying rhythmic EEG activity during sleep. In: Frank MG (ed) Brain activity in sleep. Elsevier, Amsterdam, pp 55–89
Franken P (2013) A role for clock genes in sleep homeostasis. Curr Opin Neurobiol 23(5):864–872
Franken P, Chollet D, Tafti M (2001) The homeostatic regulation of sleep need is under genetic control. J Neurosci 21:2610–2621

Franken P, Dijk DJ (2009) Circadian clock genes and sleep homeostasis. Eur J Neurosci 29:1820–1829

Franken P, Dijk DJ, Tobler I, Borbely AA (1991a) Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. Am J Physiol 261:R198–R208

Franken P, Dudley CA, Estill SJ, Barakat M, Thomason R, O'Hara BF, McKnight SL (2006) NPAS2 as a transcriptional regulator of non-rapid eye movement sleep: genotype and sex interactions. Proc Natl Acad Sci U S A 103:7118–7123

Franken P, Lopez-Molina L, Marcacci L, Schibler U, Tafti M (2000) The transcription factor DBP affects circadian sleep consolidation and rhythmic EEG activity. J Neurosci 20:617–625

Franken P, Malafosse A, Tafti M (1999) Genetic determinants of sleep regulation in inbred mice. Sleep 22:155–169

Franken P, Thomason R, Heller HC, O'Hara BF (2007) A non-circadian role for clock-genes in sleep homeostasis: a strain comparison. BMC Neurosci 8:87

Franken P, Tobler I, Borbely AA (1991b) Sleep homeostasis in the rat: simulation of the time course of EEG slow-wave activity. Neurosci Lett 130:141–144

Fredholm BB, Irenius E, Kull B, Schulte G (2001) Comparison of the potency of adenosine as an agonist at human adenosine receptors expressed in Chinese hamster ovary cells. Biochem Pharmacol 61:443–448

Garcia JA, Zhang D, Estill SJ, Michnoff C, Rutter J, Reick M, Scott K, Diaz-Arrastia R, McKnight SL (2000) Impaired cued and contextual memory in NPAS2-deficient mice. Science 288:2226–2230

Geyer H (1937) Uber den Schlaf von Zwillingen. Z Indukt Abstamm verebungsl 78:524–527

Goel N, Banks S, Lin L, Mignot E, Dinges DF (2011) Catechol-O-methyltransferase Val158Met polymorphism associates with individual differences in sleep physiologic responses to chronic sleep loss. PLoS ONE 6:e29283

Groeger JA, Viola AU, Lo JC, von Schantz M, Archer SN, Dijk DJ (2008) Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. Sleep 31:1159–1167

Gu YZ, Hogenesch JB, Bradfield CA (2000) The PAS superfamily: sensors of environmental and developmental signals. Annu Rev Pharmacol Toxicol 40:519–561

Guan Z, Peng X, Fang J (2004) Sleep deprivation impairs spatial memory and decreases extracellular signal-regulated kinase phosphorylation in the hippocampus. Brain Res 1018:38–47

Hajdu I, Obal F Jr, Fang J, Krueger JM, Rollo CD (2002) Sleep of transgenic mice producing excess rat growth hormone. Am J Physiol Regul Integr Comp Physiol 282:R70–R76

Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG (2009) Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61:213–219

Hasan S, van der Veen DR, Winsky-Sommerer R, Dijk DJ, Archer SN (2011) Altered sleep and behavioral activity phenotypes in PER3-deficient mice. Am J Physiol Regul Integr Comp Physiol 301:R1821–R1830

Hasan S, Winsky-Sommerer R, Dijk DJ, Archer SN (2012) Abstracts. J Sleep Res 21:1–387

Hayaishi O, Urade Y, Eguchi N, Huang ZL (2004) Genes for prostaglandin d synthase and receptor as well as adenosine A2A receptor are involved in the homeostatic regulation of nrem sleep. Arch Ital Biol 142:533–539

He Y, Jones CR, Fujiki N, Xu Y, Guo B, Holder JL Jr, Rossner MJ, Nishino S, Fu YH (2009) The transcriptional repressor DEC2 regulates sleep length in mammals. Science 325:866–870

Hinard V, Mikhail C, Pradervand S, Curie T, Houtkooper RH, Auwerx J, Franken P, Tafti M (2012) Key electrophysiological, molecular, and metabolic signatures of sleep and wakefulness revealed in primary cortical cultures. J Neurosci 32(36):12506–12517

Hu JH, Park JM, Park S, Xiao B, Dehoff MH, Kim S, Hayashi T, Schwarz MK, Huganir RL, Seeburg PH, Linden DJ, Worley PF (2010) Homeostatic scaling requires group I mGluR activation mediated by Homer1a. Neuron 68(6):1128–1142

Huang ZL, Urade Y, Hayaishi O (2007) Prostaglandins and adenosine in the regulation of sleep and wakefulness. Curr Opin Pharmacol 7:33–38

Huber R, Deboer T, Tobler I (2000) Effects of sleep deprivation on sleep and sleep EEG in three mouse strains: empirical data and simulations. Brain Res 857:8–19

Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78–81

Huber R, Tononi G, Cirelli C (2007) Exploratory behavior, cortical BDNF expression, and sleep homeostasis. Sleep 30:129–139

Jenkins A, Archer SN, von Schantz M (2005) Expansion during primate radiation of a variable number tandem repeat in the coding region of the circadian clock gene period3. J Biol Rhythms 20:470–472

Johnson TE, Wood WB (1982) Genetic analysis of life-span in Caenorhabditis elegans. Proc Natl Acad Sci U S A 79:6603–6607

Kalinchuk AV, McCarley RW, Porkka-Heiskanen T, Basheer R (2011) The time course of adenosine, nitric oxide (NO) and inducible NO synthase changes in the brain with sleep loss and their role in the non-rapid eye movement sleep homeostatic cascade. J Neurochem 116:260–272

Kaushal N, Ramesh V, Gozal D (2012) TNF-α and temporal changes in sleep architecture in mice exposed to sleep fragmentation. PLoS ONE 7(9):e45610

King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, Steeves TD, Vitaterna MH, Kornhauser JM, Lowrey PL, Turek FW, Takahashi JS (1997) Positional cloning of the mouse circadian clock gene. Cell 89:641–653

Klein DC, Moore RY, Reppert SM (1991) Suprachiasmatic nucleus: the mind's clock. Oxford University Press, New York

Knight J, Abbott A (2002) Full house. Nature 417:785–786

Ko CH, Takahashi JS (2006) Molecular components of the mammalian circadian clock. Hum Mol Genet 15(Spec No 2):R271–R277

Koh K, Joiner WJ, Wu MN, Yue Z, Smith CJ, Sehgal A (2008) Identification of SLEEPLESS, a sleep-promoting factor. Science 321:372–376

Kopp C, Albrecht U, Zheng B, Tobler I (2002) Homeostatic sleep regulation is preserved in mPer1 and mPer2 mutant mice. Eur J Neurosci 16:1099–1106

Kover PX, Valdar W, Trakalo J, Scarcelli N, Ehrenreich IM, Purugganan MD, Durrant C, Mott R (2009) A Multiparent advanced generation inter-cross to fine-map quantitative traits in Arabidopsis thaliana. PLoS Genet 5:e1000551

Krueger JM (2008) The role of cytokines in sleep regulation. Curr Pharm Des 14:3408–3416

Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, Panksepp J (2008) Sleep as a fundamental property of neuronal assemblies. Nat Rev Neurosci 9:910–919

Krueger JM, Clinton JM, Winters BD, Zielinski MR, Taishi P, Jewett KA, Davis CJ (2011) Involvement of cytokines in slow wave sleep. Prog Brain Res 193:39–47

Kume K, Kume S, Park SK, Hirsh J, Jackson FR (2005) Dopamine is a regulator of arousal in the fruit fly. J Neurosci 25:7377–7384

Lander ES, Botstein D (1989) Mapping mendelian factors underlying quantitative traits using RFLP linkage maps. Genetics 121:185–199

Laposky A, Easton A, Dugovic C, Walisser J, Bradfield C, Turek F (2005) Deletion of the mammalian circadian clock gene BMAL1/Mop3 alters baseline sleep architecture and the response to sleep deprivation. Sleep 28:395–409

Larkin JE, Yokogawa T, Heller HC, Franken P, Ruby NF (2004) Homeostatic regulation of sleep in arrhythmic Siberian hamsters. Am J Physiol Regul Integr Comp Physiol 287:R104–R111

Latini S, Pedata F (2001) Adenosine in the central nervous system: release mechanisms and extracellular concentrations. J Neurochem 79:463–484

Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, Boe AF, Boguski MS, Brockway KS, Byrnes EJ, Chen L, Chen L, Chen TM, Chin MC, Chong J, Crook BE, Czaplinska A, Dang CN, Datta S, Dee NR, Desaki AL, Desta T, Diep E, Dolbeare TA, Donelan MJ, Dong HW, Dougherty JG, Duncan BJ, Ebbert AJ, Eichele G, Estin LK, Faber C,

Facer BA, Fields R, Fischer SR, Fliss TP, Frensley C, Gates SN, Glattfelder KJ, Halverson KR, Hart MR, Hohmann JG, Howell MP, Jeung DP, Johnson RA, Karr PT, Kawal R, Kidney JM, Knapik RH, Kuan CL, Lake JH, Laramee AR, Larsen KD, Lau C, Lemon TA, Liang AJ, Liu Y, Luong LT, Michaels J, Morgan JJ, Morgan RJ, Mortrud MT, Mosqueda NF, Ng LL, Ng R, Orta GJ, Overly CC, Pak TH, Parry SE, Pathak SD, Pearson OC, Puchalski RB, Riley ZL, Rockett HR, Rowland SA, Royall JJ, Ruiz MJ, Sarno NR, Schaffnit K, Shapovalova NV, Sivisay T, Slaughterbeck CR, Smith SC, Smith KA, Smith BI, Sodt AJ, Stewart NN, Stumpf KR, Sunkin SM, Sutram M, Tam A, Teemer CD, Thaller C, Thompson CL, Varnam LR, Visel A, Whitlock RM, Wohnoutka PE, Wolkey CK, Wong VY et al (2007) Genome-wide atlas of gene expression in the adult mouse brain. Nature 445:168–176

Li Y, Alvarez OA, Gutteling EW, Tijsterman M, Fu J, Riksen JA, Hazendonk E, Prins P, Plasterk RH, Jansen RC, Breitling R, Kammenga JE (2006) Mapping determinants of gene expression plasticity by genetical genomics in C. elegans. PLoS Genet 2:e222

Linkowski P (1999) EEG sleep patterns in twins. J Sleep Res 8(Suppl 1):11–13

Lopez-Molina L, Conquet F, Dubois-Dauphin M, Schibler U (1997) The DBP gene is expressed according to a circadian rhythm in the suprachiasmatic nucleus and influences circadian behavior. EMBO J 16:6762–6771

Mackiewicz M, Pack AI (2003) Functional genomics of sleep. Respir Physiol Neurobiol 135:207–220

Mackiewicz M, Paigen B, Naidoo N, Pack AI (2008) Analysis of the QTL for sleep homeostasis in mice: Homer1a is a likely candidate. Physiol Genomics 33:91–99

Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI (2007) Macromolecule biosynthesis: a key function of sleep. Physiol Genomics 31:441–457

Mackiewicz M, Zimmerman JE, Shockley KR, Churchill GA, Pack AI (2009) What are microarrays teaching us about sleep? Trends Mol Med 15:79–87

Maret S, Dorsaz S, Gurcel L, Pradervand S, Petit B, Pfister C, Hagenbuchle O, O'Hara BF, Franken P, Tafti M (2007) Homer1a is a core brain molecular correlate of sleep loss. Proc Natl Acad Sci U.S.A 104:20090–20095

Maret S, Franken P, Dauvilliers Y, Ghyselinck NB, Chambon P, Tafti M (2005) Retinoic acid signaling affects cortical synchrony during sleep. Science 310:111–113

Mizoguchi A, Eguchi N, Kimura K, Kiyohara Y, Qu WM, Huang ZL, Mochizuki T, Lazarus M, Kobayashi T, Kaneko T, Narumiya S, Urade Y, Hayaishi O (2001) Dominant localization of prostaglandin D receptors on arachnoid trabecular cells in mouse basal forebrain and their involvement in the regulation of non-rapid eye movement sleep. Proc Natl Acad Sci U S A 98:11674–11679

Mongrain V, Hernandez SA, Pradervand S, Dorsaz S, Curie T, Hagiwara G, Gip P, Heller HC, Franken P (2010) Separating the contribution of glucocorticoids and wakefulness to the molecular and electrophysiological correlates of sleep homeostasis. Sleep 33:1147–1157

Mongrain V, La Spada F, Curie T, Franken P (2011) Sleep loss reduces the DNA-binding of BMAL1, CLOCK, and NPAS2 to specific clock genes in the mouse cerebral cortex. PLoS ONE 6:e26622

Mracek P, Santoriello C, Idda ML, Pagano C, Ben-Moshe Z, Gothilf Y, Vallone D, Foulkes NS (2012) Regulation of per and cry genes reveals a central role for the D-box enhancer in light-dependent gene expression. PLoS ONE 7:e51278

Naidoo N, Casiano V, Cater J, Zimmerman J, Pack AI (2007) A role for the molecular chaperone protein BiP/GRP78 in Drosophila sleep homeostasis. Sleep 30:557–565

Naidoo N, Ferber M, Galante RJ, McShane B, Hu JH, Zimmerman J, Maislin G, Cater J, Wyner A, Worley P, Pack AI (2012) Role of Homer proteins in the maintenance of sleep-wake states. PLoS ONE 7:e35174

Naidoo N, Giang W, Galante RJ, Pack AI (2005) Sleep deprivation induces the unfolded protein response in mouse cerebral cortex. J Neurochem 92:1150–1157

Naylor E, Bergmann BM, Krauski K, Zee PC, Takahashi JS, Vitaterna MH, Turek FW (2000) The circadian clock mutation alters sleep homeostasis in the mouse. J Neurosci 20:8138–8143

Neckelmann D, Ursin R (1993) Sleep stages and EEG power spectrum in relation to acoustical stimulus arousal threshold in the rat. Sleep 16:467–477

Obal F Jr, Alt J, Taishi P, Gardi J, Krueger JM (2003) Sleep in mice with nonfunctional growth hormone-releasing hormone receptors. Am J Physiol Regul Integr Comp Physiol 284:R131–R139

Obal F Jr, Fang J, Taishi P, Kacsoh B, Gardi J, Krueger JM (2001) Deficiency of growth hormone-releasing hormone signaling is associated with sleep alterations in the dwarf rat. J Neurosci 21:2912–2918

Obal F Jr, Krueger JM (2004) GHRH and sleep. Sleep Med Rev 8:367–377

Ocampo-Garcés A, Molina E, Rodríguez A, Vivaldi EA (2000) Homeostasis of REM sleep after total and selective sleep deprivation in the rat. J Neurophysiol 84:2699–2702

Palchykova S, Winsky-Sommerer R, Shen HY, Boison D, Gerling A, Tobler I (2010) Manipulation of adenosine kinase affects sleep regulation in mice. J Neurosci 30:13157–13165

Philip VM, Sokoloff G, Ackert-Bicknell CL, Striz M, Branstetter L, Beckmann MA, Spence JS, Jackson BL, Galloway LD, Barker P, Wymore AM, Hunsicker PR, Durtschi DC, Shaw GS, Shinpock S, Manly KF, Miller DR, Donohue KD, Culiat CT, Churchill GA, Lariviere WR, Palmer AA, O'Hara BF, Voy BH, Chesler EJ (2001) Genetic analysis in the Collaborative Cross breeding population. Genome Res 21:1223–1238

Popa D, El Yacoubi M, Vaugeois JM, Hamon M, Adrien J (2006) Homeostatic regulation of sleep in a genetic model of depression in the mouse: effects of muscarinic and 5-HT1A receptor activation. Neuropsychopharmacology 31:1637–1646

Porkka-Heiskanen T, Strecker RE, McCarley RW (2000) Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: an in vivo microdialysis study. Neuroscience 99:507–517

Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW (1997) Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science 276:1265–1268

Qu WM, Xu XH, Yan MM, Wang YQ, Urade Y, Huang ZL (2010) Essential role of dopamine D2 receptor in the maintenance of wakefulness, but not in homeostatic regulation of sleep, in mice. J Neurosci 30:4382–4389

Rainnie DG, Grunze HC, McCarley RW, Greene RW (1994) Adenosine inhibition of mesopontine cholinergic neurons: implications for EEG arousal. Science 263:689–692

Rechtschaffen A, Bergmann BM, Gilliland MA, Bauer K (1999) Effects of method, duration, and sleep stage on rebounds from sleep deprivation in the rat. Sleep 22:11–13

Retey JV, Adam M, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP (2007) A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. Clin Pharmacol Ther 81:692–698

Rhyner TA, Borbely AA, Mallet J (1990) Molecular cloning of forebrain mRNAs which are modulated by sleep deprivation. Eur J Neurosci 2:1063–1073

Ringwald M, Iyer V, Mason JC, Stone KR, Tadepally HD, Kadin JA, Bult CJ, Eppig JT, Oakley DJ, Briois S, Stupka E, Maselli V, Smedley D, Liu S, Hansen J, Baldock R, Hicks GG, Skarnes WC (2011) The IKMC web portal: a central point of entry to data and resources from the International Knockout Mouse Consortium. Nucleic Acids Res 39:D849–D855

Rockman MV, Kruglyak L (2009) Recombinational landscape and population genomics of Caenorhabditis elegans. PLoS Genet 5:e1000419

Roth C, Achermann P, Borbely AA (1999) Alpha activity in the human REM sleep EEG: topography and effect of REM sleep deprivation. Clin Neurophysiol 110:632–635

Rupp TL, Wesensten NJ, Newman R, Balkin TJ (2012) PER3 and ADORA2A polymorphisms impact neurobehavioral performance during sleep restriction. J Sleep Res 22(2):160–165

Rutter J, Reick M, Wu LC, McKnight SL (2001) Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. Science 293:510–514

Schmitt LI, Sims RE, Dale N, Haydon PG (2012) Wakefulness affects synaptic and network activity by increasing extracellular astrocyte-derived adenosine. J Neurosci 32:4417–4425

Seugnet L, Boero J, Gottschalk L, Duntley SP, Shaw PJ (2006) Identification of a biomarker for sleep drive in flies and humans. Proc Natl Acad Sci U.S.A 103:19913–19918
Shaw PJ, Cirelli C, Greenspan RJ, Tononi G (2000) Correlates of sleep and waking in Drosophila melanogaster. Science 287:1834–1837
Shaw PJ, Franken P (2003) Perchance to dream: solving the mystery of sleep through genetic analysis. J Neurobiol 54:179–202
Shaw PJ, Tononi G, Greenspan RJ, Robinson DF (2002) Stress response genes protect against lethal effects of sleep deprivation in Drosophila. Nature 417:287–291
Shearman LP, Jin X, Lee C, Reppert SM, Weaver DR (2000) Targeted disruption of the mPer3 gene: subtle effects on circadian clock function. Mol Cell Biol 20:6269–6275
Shiromani PJ, Xu M, Winston EM, Shiromani SN, Gerashchenko D, Weaver DR (2004) Sleep rhythmicity and homeostasis in mice with targeted disruption of mPeriod genes. Am J Physiol Regul Integr Comp Physiol 287:R47–R57
Stassen HH, Coppola R, Gottesman II, Torrey EF, Kuny S, Rickler KC, Hell D (1999) EEG differences in monozygotic twins discordant and concordant for schizophrenia. Psychophysiology 36:109–117
Stenberg D, Litonius E, Halldner L, Johansson B, Fredholm BB, Porkka-Heiskanen T (2003) Sleep and its homeostatic regulation in mice lacking the adenosine A1 receptor. J Sleep Res 12:283–290
Szumlinski KK, Kalivas PW, Worley PF (2006) Homer proteins: implications for neuropsychiatric disorders. Curr Opin Neurobiol 16(3):251–257
Taishi P, Churchill L, Wang M, Kay D, Davis CJ, Guan X, De A, Yasuda T, Liao F, Krueger JM (2007) TNFalpha siRNA reduces brain TNF and EEG delta wave activity in rats. Brain Res 1156:125–132
Takahashi Y, Ebihara S, Nakamura Y, Takahashi K (1981) A model of human sleep-related growth hormone secretion in dogs: effects of 3, 6, and 12 hours of forced wakefulness on plasma growth hormone, cortisol, and sleep stages. Endocrinology 109:262–272
Takahashi Y, Kipnis DM, Daughaday WH (1968) Growth hormone secretion during sleep. J Clin Invest 47:2079–2090
Talbot CJ, Nicod A, Cherny SS, Fulker DW, Collins AC, Flint J (1999) High-resolution mapping of quantitative trait loci in outbred mice. Nat Genet 21:305–308
Tasali E, Leproult R, Ehrmann DA, Van Cauter E (2008) Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A 105:1044–1049
Terao A, Wisor JP, Peyron C, Apte-Deshpande A, Wurts SW, Edgar DM, Kilduff TS (2006) Gene expression in the rat brain during sleep deprivation and recovery sleep: an Affymetrix GeneChip study. Neuroscience 137:593–605
Thompson CL, Wisor JP, Lee CK, Pathak SD, Gerashchenko D, Smith KA, Fischer SR, Kuan CL, Sunkin SM, Ng LL, Lau C, Hawrylycz M, Jones AR, Kilduff TS, Lein ES (2010) Molecular and anatomical signatures of sleep deprivation in the mouse brain. Front Neurosci 4:165
Tobler I, Borbely AA (1986) Sleep EEG in the rat as a function of prior waking. Electroencephalogr Clin Neurophysiol 64:74–76
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10(1):49–62
Tomioka K, Matsumoto A (2010) A comparative view of insect circadian clock systems. Cell Mol Life Sci 67:1397–1406
Trachsel L, Edgar DM, Seidel WF, Heller HC, Dement WC (1992) Sleep homeostasis in suprachiasmatic nuclei-lesioned rats: effects of sleep deprivation and triazolam administration. Brain Res 589:253–261
Ukai-Tadenuma M, Yamada RG, Xu H, Ripperger JA, Liu AC, Ueda HR (2011) Delay in feedback repression by cryptochrome 1 is required for circadian clock function. Cell 144:268–281
Urade Y, Eguchi N, Qu WM, Sakata M, Huang ZL, Chen JF, Schwarzschild MA, Fink JS, Hayaishi O (2003) Sleep regulation in adenosine A2A receptor-deficient mice. Neurology 61:S94–S96

Urade Y, Hayaishi O (2011) Prostaglandin D2 and sleep/wake regulation. Sleep Med Rev 15:411–418

Valatx JL, Bugat R (1974) Genetic factors as determinants of the waking-sleep cycle in the mouse (author's transl). Brain Res 69:315–330

Valatx JL, Bugat R, Jouvet M (1972) Genetic studies of sleep in mice. Nature 238:226–227

van Beijsterveldt CE, Molenaar PC, de Geus EJ, Boomsma DI (1996) Heritability of human brain functioning as assessed by electroencephalography. Am J Hum Genet 58:562–573

van der Horst GT, Muijtjens M, Kobayashi K, Takano R, Kanno S, Takao M, de Wit J, Verkerk A, Eker AP, van Leenen D, Buijs R, Bootsma D, Hoeijmakers JH, Yasui A (1999) Mammalian Cry1 and Cry2 are essential for maintenance of circadian rhythms. Nature 398:627–630

Van der Veen DR, Archer SN (2010) Light-dependent behavioral phenotypes in PER3-deficient mice. J Biol Rhythms 25:3–8

Vatine G, Vallone D, Appelbaum L, Mracek P, Ben-Moshe Z, Lahiri K, Gothilf Y, Foulkes NS (2009) Light directs zebrafish period2 expression via conserved D and E boxes. PLoS Biol 7:e1000223

Vienne J, Bettler B, Franken P, Tafti M (2010) Differential effects of GABAB receptor subtypes, {gamma}-hydroxybutyric Acid, and Baclofen on EEG activity and sleep regulation. J Neurosci 30:14194–14204

Viola AU, Archer SN, James LM, Groeger JA, Lo JC, Skene DJ, von Schantz M, Dijk DJ (2007) PER3 polymorphism predicts sleep structure and waking performance. Curr Biol 17:613–618

Viola AU, Chellappa SL, Archer SN, Pugin F, Gotz T, Dijk DJ, Cajochen C (2012) Interindividual differences in circadian rhythmicity and sleep homeostasis in older people: effect of a PER3 polymorphism. Neurobiol Aging 33(1010):e1017–e1027

Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, Dove WF, Pinto LH, Turek FW, Takahashi JS (1994) Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior. Science 264:719–725

Vitaterna MH, Selby CP, Todo T, Niwa H, Thompson C, Fruechte EM, Hitomi K, Thresher RJ, Ishikawa T, Miyazaki J, Takahashi JS, Sancar A (1999) Differential regulation of mammalian period genes and circadian rhythmicity by cryptochromes 1 and 2. Proc Natl Acad Sci U S A 96:12114–12119

Ward LD, Kellis M (2012) HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res 40:D930–D934

Werth E, Dijk DJ, Achermann P, Borbely AA (1996) Dynamics of the sleep EEG after an early evening nap: experimental data and simulations. Am J Physiol 271:R501–R510

Wimmer RD, Astori S, Bond CT, Rovo Z, Chatton JY, Adelman JP, Franken P, Luthi A (2012) Sustaining sleep spindles through enhanced SK2-channel activity consolidates sleep and elevates arousal threshold. J Neurosci 32:13917–13928

Winsky-Sommerer R (2009) Role of GABAA receptors in the physiology and pharmacology of sleep. Eur J Neurosci 29:1779–1794

Wisor JP, O'Hara BF, Terao A, Selby CP, Kilduff TS, Sancar A, Edgar DM, Franken P (2002) A role for cryptochromes in sleep regulation. BMC Neurosci 3:20

Wisor JP, Pasumarthi RK, Gerashchenko D, Thompson CL, Pathak S, Sancar A, Franken P, Lein ES, Kilduff TS (2008) Sleep deprivation effects on circadian clock gene expression in the cerebral cortex parallel electroencephalographic differences among mouse strains. J Neurosci 28:7193–7201

Wu MN, Ho K, Crocker A, Yue Z, Koh K, Sehgal A (2009) The effects of caffeine on sleep in Drosophila require PKA activity, but not the adenosine receptor. J Neurosci 29:11029–11037

Wu MN, Koh K, Yue Z, Joiner WJ, Sehgal A (2008) A genetic screen for sleep and circadian mutants reveals mechanisms underlying regulation of sleep in Drosophila. Sleep 31:465–472

Yalcin B, Nicod J, Bhomra A, Davidson S, Cleak J, Farinelli L, Osteras M, Whitley A, Yuan W, Gan X, Goodson M, Klenerman P, Satpathy A, Mathis D, Benoist C, Adams DJ, Mott R, Flint

J (2010) Commercially available outbred mice for genome-wide association studies. PLoS Genet 6(9):e1001085

Yamajuku D, Shibata Y, Kitazawa M, Katakura T, Urata H, Kojima T, Nakata O, Hashimoto S (2010) Identification of functional clock-controlled elements involved in differential timing of Per1 and Per2 transcription. Nucleic Acids Res 38:7964–7973

Yamajuku D, Shibata Y, Kitazawa M, Katakura T, Urata H, Kojima T, Takayasu S, Nakata O, Hashimoto S (2011) Cellular DBP and E4BP4 proteins are critical for determining the period length of the circadian oscillator. FEBS Lett 585:2217–2222

Yoshida H, Peterfi Z, Garcia-Garcia F, Kirkpatrick R, Yasuda T, Krueger JM (2004) State-specific asymmetries in EEG slow wave activity induced by local application of TNFalpha. Brain Res 1009:129–136

Zielinski MR, Taishi P, Clinton JM, Krueger JM (2012) 5'-Ectonucleotidase-knockout mice lack non-REM sleep responses to sleep deprivation. Eur J Neurosci 35:1789–1798

Zimmerman JE, Naidoo N, Raizen DM, Pack AI (2008) Conservation of sleep: insights from non-mammalian model systems. Trends Neurosci 31:371–376

Zimmerman JE, Rizzo W, Shockley KR, Raizen DM, Naidoo N, Mackiewicz M, Churchill GA, Pack AI (2006) Multiple mechanisms limit the duration of wakefulness in Drosophila brain. Physiol Genomics 27:337–350

Sleep Deprivation and Gene Expression

Annie da Costa Souza and Sidarta Ribeiro

Abstract Sleep occurs in a wide range of animal species as a vital process for the maintenance of homeostasis, metabolic restoration, physiological regulation, and adaptive cognitive functions in the central nervous system. Long-term perturbations induced by the lack of sleep are mostly mediated by changes at the level of transcription and translation. This chapter reviews studies in humans, rodents, and flies to address the various ways by which sleep deprivation affects gene expression in the nervous system, with a focus on genes related to neuronal plasticity, brain function, and cognition. However, the effects of sleep deprivation on gene expression and the functional consequences of sleep loss are clearly not restricted to the cognitive domain but may include increased inflammation, expression of stress-related genes, general impairment of protein translation, metabolic imbalance, and thermal deregulation.

Keywords Sleep · Gene expression · Immediate early genes · Cognition · Memory · Inflammation · Stress · Thermoregulation

Contents

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1 Introduction

Sleep is a complex behavioral state of major importance for vertebrates (Frank 2012) and invertebrates (van Swinderen 2007; Ramon et al. 2012), which directly or indirectly affects a plurality of physiological functions (Shaw et al. 2000; Markwald et al. 2013; Kayser et al. 2014). While moderate sleep disturbance leads to stress and homeostasic imbalance (Killick et al. 2012; Pellegrino et al. 2012; Moller-Levet et al. 2013; Gonnissen et al. 2013), controlled laboratory studies in rodents have shown that prolonged sleep deprivation causes serious physiological and immunological deficits, eventually causing death (Rechtschaffen et al. 1983; Bergmann et al. 1989a; Everson et al. 1994).

Since sleep-dependent gene regulation produces long-term changes in behavior and physiology, it is important from a clinical point of view to understand how sleep deprivation affects health through the expression of specific genes (Tononi et al. 1994; Ledoux et al. 1996; Cirelli and Tononi 2000b; Tononi and Cirelli 2001; Cirelli 2002; Terao et al. 2003, 2006; Nelson et al. 2004; Cirelli et al. 2005; Maret et al. 2007; Jones et al. 2008; Thompson et al. 2010; Nitabach et al. 2011). Conversely, the investigation of sleep-dependent gene regulation has overarching implications for basic research on the mechanisms underlying cognition, neurogenesis, thermal balance, inflammation, metabolic turnover, and several other processes (Smith and Kelly 1988; Everson 1995; Taishi et al. 2001; Guzman-Marin et al. 2003, 2005, 2006; Knutson et al. 2007; Guess et al. 2009; Mullington et al. 2009; Tufik et al. 2009; van Leeuwen et al. 2009; Calegare et al. 2010; Aldabal and Bahammam 2011; Barf et al. 2012; Aydin et al. 2013). In this chapter, we review studies concerned with how sleep deprivation affects gene expression, with a focus on genes involved in neuronal plasticity, brain function and cognition.

It is important to note that several of the studies reviewed here have assessed protein levels rather than changes in gene expression per se. The transcription of mRNA from DNA and the translation of protein from mRNA are subjected to complex regulation by a variety of mechanisms (Filipowicz et al. 2008; Maas 2010; McManus and Graveley 2011). Since mRNA and protein levels related to the same gene are often separately regulated (Vogel and Marcotte 2012), protein measurements are not necessarily good indicators of gene expression. On the other hand, changes in protein levels are more indicative of an effective genomic response than

changes in the amount of mRNA transcripts. For these reasons, we opted to review the literature more broadly, while making explicit for each study reviewed whether gene expression and/or protein levels were assessed.

2 Approaches to Study Effects of Sleep Deprivation on Gene Expression

2.1 Methods of Sleep Deprivation

To study the role of sleep and the effects of sleep loss on gene expression, a wide variety of methods has been employed to deprive animals of their sleep for variable durations. While each of these methods is aimed at keeping animals awake, there are method-specific effects that need to be considered when discussing the resulting changes in gene expression, because of different impacts on specific sleep states, and different side effects.

2.1.1 Flowerpot Method (or Disk-over-water)

The flowerpot method, basis of a modified (automatized) version called disk-over-water method, was first proposed by Michel Jouvet as a reliable way to systematically deprive animals from sleep (Jouvet et al. 1964; Kushida et al. 1989; Rechtschaffen and Bergmann 1995). The method consists in putting the animal on a small platform, typically a disk, within a tank of water. In the flowerpot method, the animal has to maintain wakefulness in order to stay on top of the disk, because upon entering sleep there is a loss of muscle tone and the animal falls in the water, interrupting sleep. Specific deprivation of rapid-eye-movement sleep (REM) can be achieved by slightly increasing the area of the circular platform [in rats, from 6.5 cm of diameter (Mendelson et al. 1974) to 11 cm of diameter (Kushida et al. 1989; Youngblood et al. 1997)], thus allowing animals to traverse slow-wave sleep (SWS)—in which there is residual muscle tone (Jouvet 1967)—but not REM (Jouvet et al. 1964; Mendelson et al. 1974; Jouvet 1994). The use of larger platforms that allow for sleep serves to generate negative controls (Youngblood et al. 1997). In the disk-over-water method, early signs of sleep trigger a slow rotation of the disk, carrying the animal to a pool of water; animals learn to wake up and move away from the water, thus interrupting sleep. This method can be used for specific REM sleep deprivation or for total sleep deprivation (Bergmann et al. 1989a, b; National Research Council of the National Academies 2003). These methods are highly efficient for unsupervised sleep deprivation, but are associated with various confounding factors and high levels of stress, associated with restricted movement and the risk of falling in the water surrounding the platform. Mice are less impacted by movement restrictions in the flowerpot method because they can use the metal grids on cage tops to move around (Bergmann et al. 1989b; National Research Council of the National Academies 2003). In rats,

which typically cannot perform this behavior, several platforms are used to mitigate the stress associated with movement restriction (Alkadhi et al. 2013).

2.1.2 Treadmills and Rotating Wheels

Another common procedure to keep animals awake is the use of motorized treadmills or wheels (Guzman-Marin et al. 2005, 2006; Roman et al. 2005; Xu et al. 2010). This approach is thought to be less stressful than the flowerpot method, but the continuous forced activity, even though it is generally at a rather slow pace, may have effects unrelated to sleep loss per se. A commonly used control procedure is to have animals that walk at a faster pace for shorter periods of time, allowing them sufficient sleep (Guzman-Marin et al. 2005, 2006; Roman et al. 2005).

2.1.3 Cage Tapping and Gentle Handling

A supervised method for sleep deprivation commonly used in rodents consists of tapping the experimental cage or gently handling the animal as soon as a specific sleep state is detected (Rechtschaffen et al. 1999). This method is considered to be one of the least stressful ways of sleep deprivation, partly because animals most often remain in their home cage, and several studies have reported only minimal increases in stress hormones such as glucocorticoids (van der Borght et al. 2006; Hagewoud et al. 2010a, b, c). However, a clear disadvantage is that this method requires constant human supervision and is therefore generally used only for short sleep deprivations (Rechtschaffen et al. 1999).

2.1.4 Novel Object Presentation

This method typically consists of introducing novel objects in the experimental cage and is based on the natural tendency of rodents to explore the environment, particularly when it contains novel stimuli (Henderson 1970; Ennaceur and Delacour 1988). The disturbance caused by introducing novel objects in the cage typically induces wakefulness, as the animal is prone to spontaneously explore the objects. When an object is no longer novel, and the animal becomes drowsy, another object is introduced in the cage (Cirelli and Tononi 2000b). The main advantage of this method is that sleep is prevented due to an endogenous drive to explore a novel environment, rather than an external perturbation of the animal itself. On the other hand, well-balanced controls are nearly impossible to achieve, due to the intrinsic variability of the behavioral responses to novel object exposure (Thor et al. 1988; Dellu et al. 1996; Bevins et al. 1997; Kabbaj and Akil 2001; Pisula and Siegel 2005; Clinton et al. 2010; Duclot et al. 2011). Moreover, one caveat that must be taken into account is the fact that gene expression following a period of sleep deprivation by exposure to novel objects will confound the effects of novel object exploration with the effects of sleep loss per se.

2.1.5 Automated deprivation based on the computer analysis of neural and muscle signals

Sleep deprivation can be improved by the use of a feedback computer system for triggering cage movements depending on pre-established thresholds of neural and muscular activity (Ocampo-Garces et al. 2000; Vivaldi et al. 2008; Wu et al. 2011). In addition to the visual inspection of behavior, electrophysiological signals such as intracerebral local field potentials (LFPs) or cortical electroencephalogram (EEG) can be used to inform the experimenter about when to interfere with the animal. For instance, once the animal begins to sleep, the EEG is characterized by waves with higher amplitude and lower frequencies in comparison with the waking state; this slow-wave activity within the delta range (<4 Hz) is characteristic of SWS. In the case of REM sleep, the presence of hippocampal theta rhythm (4–10 Hz) is one of the most reliable electrophysiological signals (Franken et al. 1991). The method is suitable for the use of yoked controls, i.e., animals recorded in parallel in which the perturbations occur at approximately the same times, but uncoupled from the wake–sleep states. Computer software can identify either SWS or REM and then prompt a mechanical perturbation of the animal, typically a sudden movement of the entire cage or recording box. Such automatic supervision is very precise and reliable, allowing for the use of yoked controls as explained above, but improved with the precise and instantaneous perturbations of both experimental and control animals (Rechtschaffen et al. 1999). The main disadvantage of the method is the more expensive and sophisticated setup.

2.2 Methods for the Assessment of Gene Expression and Protein Levels

2.2.1 In Situ Hybridization

This technique uses a complementary DNA or RNA strand to detect a certain sequence of mRNA or DNA in the tissue, which for instance may be an entire brain section. Labeling can be radioactive or antigen based, using fluorophores or chromophores (Gall and Pardue 1969; Jin and Lloyd 1997). The method is suitable for determining cell-specific and region-specific changes in gene expression directly on brain sections.

2.2.2 Reverse Transcriptase Quantitative Polymerase Chain Reaction (RT-qPCR)

One important variation of classical polymerase chain reaction (PCR) is quantitative PCR (qPCR), which precisely quantifies DNA sequences (Bustin et al. 2005). A second very important variation broadly used for gene expression detection is RTq-PCR. Instead of DNA, this method amplifies mRNA sequences using reverse

transcriptase, polymerizing cDNA sequences as a product of the reaction. This method is very sensitive and also quantitative, allowing for the assessment of the amount of mRNA of a certain gene even if it is expressed at very low levels (Shiao 2003; Bustin et al. 2005); however, the method is performed on tissue homogenates and therefore allows for less regional specificity.

2.2.3 DNA Hybridization Array (Microarray)

This method uses a plate with multiple spots that contain different DNA sequences for genes of interest. These sequences are hybridized with cDNA or cRNA extracted from a tissue sample. Hybridization levels can be detected by chemiluminescence or by the use of fluorophores. Typically, an important step before hybridization is the labeling of target sequences of the sample; mRNA is purified and submitted to RT-PCR to synthesize cDNA, which is labeled afterward with a fluorescent component (Freeman et al. 2000). The main advantage of this method is the ability to assess a very large number of genes for a single tissue sample.

2.2.4 Western Blotting

This method is used to detect and sort specific proteins in tissue homogenates using gel electrophoresis. After being separated, proteins are transferred to a membrane (e.g., nitrocellulose), treated with a protein-rich blocking reagent to avoid non-specific labeling, incubated with a primary antibody (IgG) to detect a specific protein of interest, washed and then incubated with a secondary antibody (anti-IgG) associated with a reporter molecule (e.g., horseradish peroxidase or alkaline phosphatase). Detection is performed using a chromogenic or luminescent substrate (Gallagher et al. 2004). This method detects proteins and therefore provides only an indirect measurement of gene expression.

2.2.5 Immunohistochemistry

This method uses the same principle of antibody detection described above, but in tissue sections instead of homogenate samples (Jin and Lloyd 1997). This method also detects proteins and therefore provides only an indirect measurement of gene expression.

3 Sleep Deprivation and Gene Expression

Some of the most important effects of sleep deprivation are modifications in gene expression, which can reflect the activation or suppression of cellular processes leading to changes in neuronal function and synaptic connections. The analysis of

gene expression changes provides therefore a privileged window into brain function. As described in Sect. 2, there are different methods for the sleep deprivation of animal and many ways to measure changes in gene expression profiles. Most of the studies on sleep deprivation that aim to analyze gene expression are performed in rodents (Pompeiano et al. 1992, 1997; Cirelli et al. 1995, 2006; Maloney et al. 2002; Cirelli 2006; Terao et al. 2006), but there are also important studies in flies (Wang et al. 2010), birds (Jones et al. 2008), and fish (Appelbaum et al. 2010). Sleep deprivation studies are often difficult to compare, due to the use of different deprivation methods, durations, and animal models. There is also considerable variation in the methods employed to quantify gene expression levels (Fig. 1). For instance, the decision to measure protein or mRNA may bias toward different outcomes, depending on the timescale of the experiment. Since mRNA transcriptional regulation precedes protein synthesis, experimental designs must carefully consider whether the method of choice for gene expression assessment is compatible with the temporal windows chosen.

Most of the gene expression studies use the microarray method, which allows for the simultaneous measurement of large numbers of genes [from 10,000 transcripts (Cirelli and Tononi 2000b) to more than 26,000 (Cirelli et al. 2006)]. Such screens reveal that sleep deprivation causes major changes in gene expression not only in the brain but also in the periphery. Stress response genes are frequently targeted in sleep deprivation experiments, since many methods of sleep deprivation are considered stressful due to the use of unpleasant stimuli (e.g., disk-over-water method). Sleep deprivation per se may be considered a stressful situation, irrespective of which deprivation method is used. Under this assumption, sleep loss is expected to always trigger a stress response.

Several genes expressed during spontaneous waking have their expression upregulated in the central nervous system during sleep deprivation (Cirelli et al. 2006). These genes comprise immediate early genes that encode transcription factors, growth factors, adhesion molecules, neurotransmitter receptors and transporters, and enzymes (Cirelli and Tononi 2000a, b, c). A gene screen study (Cirelli and Tononi 2000b) showed a wide range of genes whose expression is upregulated by sleep deprivation: the activity-regulated cytoskeleton-associated protein (*Arc*), the C/EBP homology protein (CHOP), the immediate early response 5 (*IER*5), the nerve growth factor-induced protein A (*NGFI-A*, homologue of *Zif-268*, *Krox-24*, *Egr-1,* and *ZENK*), the nerve growth factor-induced gene B (*NGFI-B*, also known as Nr4a1), the neuroblastoma ras oncogene (*N-Ras*), the signal transducer and activator of transcription (3*Stat*3), the glucose type I transporter (*Glut*1), the VGF nerve growth factor inducible (*Vgf*), brain-derived neurotrophic factor (*BDNF*), the tyrosine-related kinase B (*TrkB*, also known as *NTRK2*), the coagulation factor III (*F*3), the binding immunoglobulin protein (*BiP*, also known as HSPA5 or HSP70), the endoplasmic reticulum resident protein 72 (*ERP*72, also known as PDIA4), the 75-kDa glucose-regulated protein (*GRP*75, also known as HSPA9), the 60-kDa heat-shock protein (*HSP*60), the 70-kDa heat-shock protein (*HSP*70), chromogranin C, synaptotagmin IV, the adrenergic receptors α and β, the GABA receptor B, the glutamate NMDA receptors 1A, 2A, and 3A, the glutamate AMPA receptors

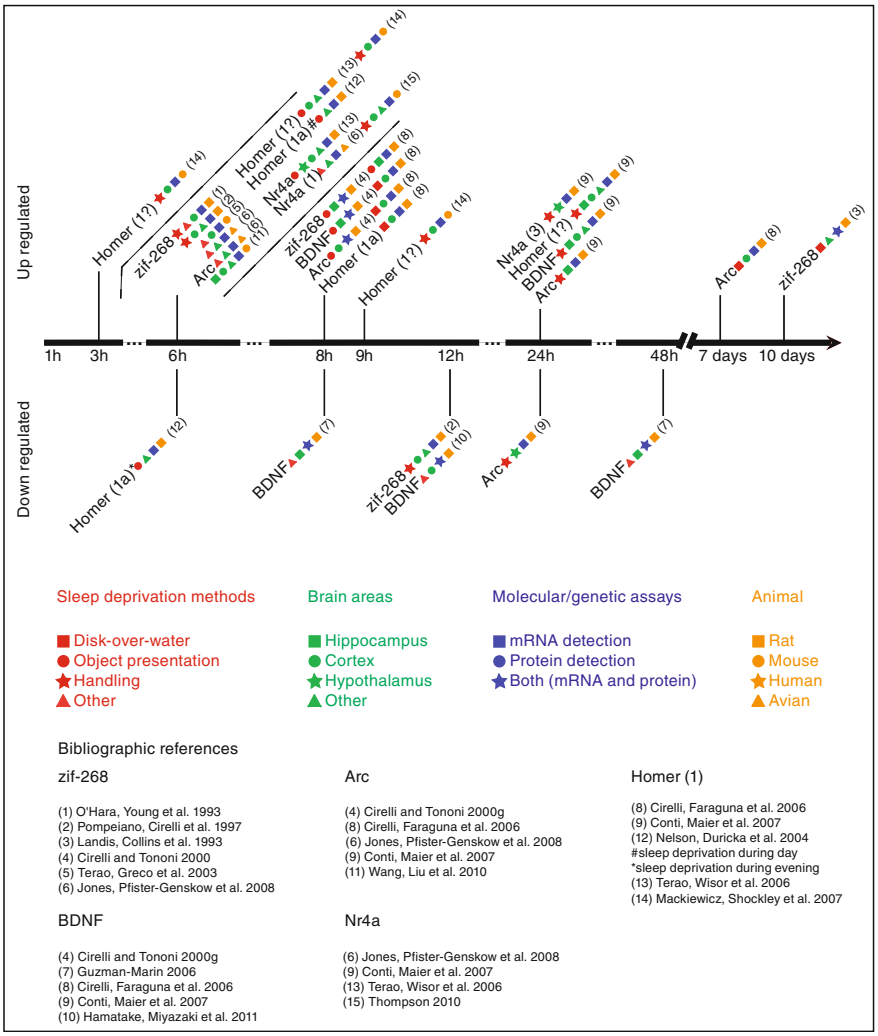

Fig. 1 Effects of sleep deprivation on plasticity-related gene expression. Symbols indicate different sleep deprivation methods, brain areas, targets of detection assays, and animal models used (respectively, polygons in *red*, *green*, *blue,* and *orange*). References listed at the *bottom* are referred as smaller numbers in parentheses (larger numbers or letters in parentheses refer to gene/protein family, while *question marks* indicate unspecified form, e.g., Homer1a, b or c)

GluR2 and GluR3, nicotinic acetylcholine receptor B, the thyroid hormone receptor beta (TRb), the glutamate/aspartate transporter (*GLAST*), and the Na/Cl transporter NTT4/Rxt1. Also upregulated are the enzymes aryl sulfotransferase, c-jun N-terminal kinase 1, serum/glucocorticoid-induced serine/threonine kinase, calmodulin, cyclin D2, LIM domain only protein 4 (LMO-4), and metallothionein 3. All these genes were systematically investigated through mRNA differential display and

cDNA microarrays, being upregulated in rats deprived of sleep for 8 h (Cirelli and Tononi 2000b). Another study from the same research group assessed the long-term effects of sleep deprivation on mRNA levels in the rat cerebral cortex. After 1 week of sleep deprivation, 75 transcripts had their levels increased in comparison with the levels found in spontaneously awake animals, as well as animals deprived of sleep for a few hours. These transcripts comprised mRNA for immunoglobulins, stress response proteins, minoxidil sulfotransferase, globins, and cortistatin. Altogether, these results indicate that sleep deprivation induces marked inflammatory and stress responses in the brain (Cirelli et al. 2006).

4 Sleep Deprivation and Early Changes in Gene Expression

Sleep deprivation upregulates the expression of several immediate early genes, as well as alternative splice variants induced by neuronal activity, whose protein products are involved in regulating a wide variety of cellular processes that ultimately influence neuronal plasticity and brain function (Tischmeyer and Grimm 1999).

4.1 c-fos

The immediate early gene c-fos gives rise to the fos protein that acts as a rather general transcription factor. Expression of the fos gene is upregulated by membrane depolarization and therefore widely used as a general marker of neuronal activity (Kovacs 1998; Cirelli and Tononi 2000c). The expression of c-fos is upregulated in several brain areas by spontaneous wakefulness (Pompeiano et al. 1994) as well as forced sleep deprivation (Cirelli et al. 1995). Both the mRNA and the protein levels of c-fos are elevated in rats when the sleep cycle is arrested, with a wide anatomical distribution that comprises the cerebral cortex, portions of the hypothalamus, the medial preoptic area, thalamic nuclei, and nuclei of the dorsal pontine tegmentum (Cirelli et al. 1995). Somewhat similar results were obtained in cats using immunohistochemistry, which revealed increased c-fos levels in the preoptic area and lateral hypothalamus of sleep-deprived animals (Ledoux et al. 1996). In mice subjected to sleep deprivation for 6h, c-fos mRNA levels were increased in the cerebral cortex, basal forebrain, thalamus, and cerebellum (Terao et al. 2003). A study of sleep deprivation in neonate rats found increased c-fos mRNA levels in the cerebral cortex and hippocampus at postnatal days 16, 20, and 24, with a return to basal levels after a 2-h recovery sleep period (Hairston 2004).

An anatomically comprehensive study of sleep-deprived mice used laser microdissection and cDNA microarrays to show upregulation of c-fos mRNA levels in visual and caudal somatosensory cortex, agranular insular cortex, orbitofrontal cortex, piriform cortex, amygdala, dorsal caudate putamen, and cerebellum, with downregulation in the ventral posteromedial nucleus of the thalamus. C-fos

expression was largely coincident with expression of the excitatory neuron-specific vesicular glutamate transporter 1 (Slc17a7) and overlapped with Arc and Nr4a1 expression in visual and agranular insular cortices (Thompson et al. 2010).

Sleep deprivation of non-mammalian vertebrates by and large yields similar results. In the white-crowned sparrow, c-fos mRNA levels are increased in several portions of the telencephalon after 6 h of sleep deprivation (Jones et al. 2008). In the zebrafish, sleep deprivation for 3 h or 6 h leads to c-fos mRNA upregulation in the olfactory bulb, telencephalon, diencephalon, and rhombencephalon, with a return to basal levels after recovery sleep (Appelbaum et al. 2010).

4.2 Zif-268

The transcription factor Zif-268 (zinc finger protein 268) is also known as NGFI-A (nerve growth factor-induced protein A), Egr-1 (early growth response protein 1), Krox-24, and ZENK (acronym of the initial letters of Zif-268, Egr-1, NGFI-A, and Krox-24). The Zif-268 protein regulates the expression of many genes involved with plasticity, mitogenesis, and differentiation, including synapsins I and II, and synaptobrevin II (Knapska and Kaczmarek 2004). Zif-268 was found to be upregulated after 6 h of sleep deprivation in the rat cerebral cortex assessed through Northern blotting (O'Hara et al. 1993). In rats submitted to sleep deprivation for up to 10 days using the disk-over-water method (Landis et al. 1993), immunocytochemistry and Northern blotting showed elevated Zif-268 expression in the dorsal raphe, lateral habenula, superior colliculus, and ventral periaqueductal gray. These neuroanatomical locations were not corroborated by a subsequent study, which applied in situ hybridization to brains of animals subjected to sleep deprivation by gentle handling for 3, 6, 12, and 24 h (Pompeiano et al. 1997). Increased mRNA levels were found in the cerebral cortex and caudate–putamen (Pompeiano et al. 1997). The same authors found that 3 h of sleep deprivation were associated with increased Zif-268 levels in the cerebral cortex but not in the locus coeruleus, while 12 or 24 h of sleep deprivation induced Zif-268 expression in the locus coeruleus, the parabrachial nuclei, and the superior and inferior colliculi (Tononi et al. 1994). A plausible explanation for the somewhat divergent findings may reside in the different amounts of sleep deprivation applied. Longer periods of deprivation may trigger self-regulation mechanisms such as the negative feedback enabled by the Zif-268 response, in which the protein recognizes consensus sequences in the promoter region of the gene, allowing for downregulation of its own expression (Christy and Nathans 1989).

More recently, a study in mice showed that sleep deprivation for 6 h followed by a recovery period of 4 h leads to the upregulation of Zif-268 mRNA levels in the cerebral cortex and basal forebrain (Terao et al. 2003). The deprivation-related increase of Zif-268 levels seems to obey very similar dynamics in the avian brain. In white-crowned sparrows, telencephalic Zif-268 mRNA levels were reported to increase 117 % after 6 h of sleep deprivation, with a 90 % increase from spontaneous waking to control (Jones et al. 2008).

4.3 Arc

Another immediate early gene involved in neuronal plasticity and affected by sleep deprivation is Arc (also known as Arg3.1), encoded by mRNA transported to post-synaptic dendritic terminals for local translation (Lyford et al. 1995). Arc participates in synaptic remodeling by regulating the dynamics of F-actin, AMPA receptors, and Ca2+/calmodulin-dependent protein kinase II (CaMKII) (Bramham et al. 2010; Okuno et al. 2012).

Arc levels are upregulated in rats after both acute (8 h) (Cirelli and Tononi 2000b) and chronic (1-week) sleep deprivation, when assessed by microarrays and confirmed by (RT-qPCR) and RNase protection assay (RPA) (Cirelli et al. 2006). Another study found Arc mRNA levels to be upregulated in the cerebral cortex of mice and rats subjected to sleep deprivation for 6 h (Terao et al. 2006). Similar results were obtained in the cerebral cortex and hippocampus after 8 h of sleep deprivation in rats, with recovery to basal Arc mRNA levels after 2 h of sleep (Taishi et al. 2001). Corroborating these findings, a study with C57BL/6J mice showed higher levels of Arc mRNA in the hippocampus, amygdala, neocortex, and piriform cortex of sleep-deprived animals, in comparison with controls. However, increased Arc levels were detected even after a 4-h sleep rebound period (Thompson et al.2010). Another study in rats using gene chip analysis and 24 h of sleep deprivation by gentle handling found a 1.2-fold decrease of Arc mRNA levels in the hypothalamus and a twofold increase in the hippocampus, in comparison with controls (Conti et al. 2007). A meta-analysis of datasets comprising 91 different genes found Arc mRNA to be upregulated in the cerebral cortex, hippocampus, olfactory bulb, and striatum of mice deprived of sleep for 6 h (Wang et al. 2010). Similar effects occur in the brain of the white-crowned sparrow, with a 66 % increase in Arc mRNA levels after 6 h of sleep deprivation (Jones et al. 2008).

4.4 Homer

Another gene of interest is Homer1, which is widely expressed in the brain and other tissues with two main splice variants: a short form called Homer1a, which is induced by neuronal activity, and long forms called Homer1b and c, which have constitutive expression (Shiraishi-Yamaguchi and Furuichi 2007). Homer1a inhibits the scaffolding action of the long forms, decreasing glutamatergic signaling and diminishing dendritic spines (Tu et al. 1998). Like Arc (Sect. 4.3), Homer1a is broadly upregulated in the brains of sleep-deprived rats (Cirelli et al. 2006; Maret et al. 2007). Additionally, it is expressed in spontaneously awake rats, which suggests that Homer1a is generally associated with wakefulness and neuronal activity (Thompson et al.2010). Homer1a mRNA is upregulated in the somatosensory cortex of rats deprived of sleep for 6 h during the day (sleep period); in contrast, Homer1a gene expression is downregulated by sleep deprivation during

the evening (active period); similar results of a lesser magnitude were obtained for Homer1bc (Nelson et al. 2004). Homer1a is significantly overexpressed in the cerebral cortex, hippocampus, and striatum in three different mouse genotypes (Maret et al. 2007). Another study using microarray analysis and the disk-over-water method presented compatible results: Rats deprived of sleep for 8 h showed upregulated Homer1a levels in comparison with animals allowed to sleep, while sleep deprivation for 7 days yielded a non-significant tendency for transcriptional downregulation in comparison with short-term sleep deprivation (8 h) and spontaneous waking (Cirelli et al. 2006). Homer1 upregulation was detected in the basal forebrain and cerebral cortex of rats submitted to sleep deprivation by introducing novel objects and tapping the cage during 6 h (Terao et al. 2006). Another study used in situ hybridization to detect Homer1 upregulation in rats deprived of sleep for 24 h (Conti et al. 2007). An investigation of Homer1 expression after 3, 6, 9, and 12 h of sleep deprivation found transcriptional upregulation in the cerebral cortex for all these periods (Mackiewicz et al. 2007). Although these particular three studies (Conti et al. 2007; Terao et al. 2006; Mackiewicz et al. 2007) did not specify which Homer1 variation was measured, it is likely that it was Homer1a, since most of the other studies cited in this section specifically indicate Homer1a to be upregulated by sleep deprivation. A meta-analysis found Homer1a levels to be upregulated in mice after 6 h of sleep deprivation in the cerebral cortex, hippocampus, olfactory bulb, and striatum (Wang et al. 2010). Interestingly, experiments performed in Drosophila melanogaster showed Homer downregulation in sleep-deprived flies. Homer1a uncouples the metabotropic glutamate receptor from other Homer isoforms. Drosophila has only one Homer isoform, which acts in the opposite direction of Homer1a (Zimmerman et al. 2006; Mackiewicz et al. 2008).

4.5 Nr4a

Gene expression is highly influenced by nuclear receptors that act as transcription factors upon activation by steroid and thyroid hormones, among other ligands (Green and Chambon 1988; McKenna and O'Malley 2002). Some nuclear receptors are regulated as immediate early genes, such as the NR4A subfamily of orphan receptors that include (NGFIB/NR4a1), the nuclear receptor-related protein 1 (NURR1/NR4a2), and the neuron-derived orphan receptor 1 (NR4a3/NOR1) (Maxwell and Muscat 2006; Hawk and Abel 2011). Sleep deprivation affects Nr4a expression, which is activated by the same calcium-dependent factors that upregulate the memory-related IEG expression reviewed above (Hawk and Abel 2010). In 6 h sleep-deprived rats, Nr4a mRNA levels were found to be upregulated in the cerebral cortex, basal forebrain, and hypothalamus (Terao et al. 2006). Another study using gene chip analysis found a 100 % increase in Nr4a3 mRNA expression in the rat hypothalamus after 24 h of sleep deprivation (Conti et al. 2007). In white-crowned sparrows

deprived of sleep for 6 h, Nr4a1 mRNA levels in the telencephalon were found to be increased by 60 %, in comparison with control animals allowed to sleep (Jones et al. 2008). An assessment of Nr4a1 gene expression in mice deprived of sleep for 6 h using laser microdissection and microarray hybridization found elevated mRNA levels in the amygdala and in the primary visual, agranular insular, orbitofrontal and piriform cortices, as well as in the cerebellum and putamen; controls allowed to sleep showed increased levels of Nr4a1 and Arc in the rostral and ventral caudate–putamen, as well as in the motor and rostral somatosensory cortices; sleep-deprived mice showed Nr4a1 upregulation in the caudal dorsolateral putamen, overall a very similar profile found for Arc expression. (Thompson et al. 2010). A meta-analysis of microarray data in mouse, rat, sparrow, and fly identified the Nr4a gene family as conserved genes affected by sleep deprivation (Wang et al. 2010).

The upregulation of immediate early gene expression by sleep deprivation requires the involvement of secondary messengers. An investigation of the levels of phosphorylated cAMP response element-binding protein (p-CREB) after 3 h of sleep deprivation detected a significant and widespread increase in the cerebral cortex (Cirelli and Tononi 2000a). Another study found the mRNA levels of CaMKII to be upregulated in the cerebral cortex and basal forebrain of rats deprived of sleep for 6 h (Terao et al. 2006). In contrast, other researchers found that 48 h of sleep deprivation reduces CREB mRNA levels to the levels found in controls kept in their home cages; similar results were obtained for CaMKII (Guzman-Marin 2006). Chemical lesions of the noradrenergic system showed that the expression of Zif-268 and c-fos during wakefulness depends critically on the integrity of the locus coeruleus (Cirelli et al. 1996). The implication of this finding is that calcium-dependent immediate early gene expression, and presumably upstream events such as increases in cAMP and p-CREB levels, also requires noradrenergic modulation.

5 Sleep Deprivation and Neurotrophic Factors

The gene expression and protein levels of neurotrophic factors involved with cell growth and function (Boyd and Gordon 2003a, b) have also been shown to be affected by sleep deprivation (Cirelli and Tononi 2000a; Sei et al. 2000; Fujihara et al. 2003; Hamatake et al. 2011; Ventskovska et al. 2014; Wallingford et al. 2014; Zielinski et al. 2014). Most studies were concerned with BDNF, a neurotrophin of great importance for neuronal plasticity and survival (Ghosh et al. 1994; Ventimiglia et al. 1995; Lipsky and Marini 2007; Sossin and Barker 2007). A study of rats selectively deprived of REM sleep for 6 h found BDNF protein levels to be unchanged in the hippocampus and decreased in the cerebellum and brain stem (Sei et al. 2000). A lack of hippocampal change in BDNF mRNA levels after sleep deprivation was also reported in rats subjected to full sleep deprivation for 8 h; in

contrast, the same animals showed a significant increase in BDNF mRNA levels in the cerebral cortex (Taishi et al. 2001). Rats subjected to sleep deprivation (for 8 and 48 h) by an intermittent treadmill method showed a significant decrease of mRNA and protein BDNF levels in the hippocampus, but not in the cerebral cortex (Guzman-Marin 2006). A different study of sleep deprivation in rats detected a significant increase of BDNF mRNA levels in the cerebral cortex (Cirelli and Tononi 2000a). Interestingly, BDNF mRNA levels were significantly increased in the cerebral cortex when animals were sleep deprived for 8 h by introducing new objects in the cage, but not in animals deprived of sleep for 1 week using the disk-over-water method (Cirelli et al. 2006). While this comparison is imperfect, varying both the duration and the method for sleep deprivation, it suggests that deprivation by cognitive challenge may impact gene expression quite differently from deprivation due to non-cognitive physiological challenge.

An investigation of sleep deprivation using gene chip methodology and in situ hybridization found BDNF mRNA levels to be upregulated in the piriform cortex, dorsal endopiriform nucleus, and hippocampus (Conti et al. 2007). Another study used microarrays and RT-PCR to show that BDNF mRNA levels are increased in the rat cerebral cortex after 96 h of REM sleep deprivation, with a return to basal levels after 24 h of sleep recovery (Guindalini et al. 2009). In neonate rats deprived of sleep for up to 180 min, mRNA BDNF levels were increased in the cerebral cortex at postnatal days P20 and P24 (Hairston 2004). Interpretation of the somewhat divergent results is complicated by differences in the methods employed for sleep deprivation, (e.g., the introduction of new objects *versus* intermittent locomotion on a treadmill), in the duration of the deprivation protocols, in the brain region analyzed, and in the age of the animals.

If the corpus of published studies on BDNF and sleep deprivation fails to systematically cover the parameter space, investigation of other neurotrophins is even sparser. Sei et al. compared the effects of 6 h of REM sleep deprivation on BDNF and nerve growth factor (NGF) protein levels in the rat hippocampus, cerebellum, and brainstem. NGF levels were significantly decreased in the hippocampus, but were unchanged in the cerebellum and brainstem (Sei et al. 2000). Another study showed that 6 h of total sleep deprivation was associated with a significant increase in the number of NGF-immunoreactive cortical neurons in the mice barrel field (Brandt et al. 2001). An investigation of the diurnal variations of neurotrophin-3 (NT-3) and BDNF levels in several brain regions of juvenile rats (2 weeks) detected increased BDNF levels in the dark phase and decreased levels in the light phase. NT-3 levels showed the opposite profile in the neocortex (Hamatake et al. 2011). Another study observed that intracerebroventricular injections of NT-3 and neurotrophin-4 (NT-4) in adult rabbits promote non-REM sleep in a dose-dependent manner (Kushikata et al. 2003). A great deal of additional experimentation is needed to elucidate the effect of sleep deprivation on neurotrophin expression.

6 Sleep Deprivation Changes Expression of Genes Related to Protein Synthesis

A microarray study of mice subjected to sleep deprivation for 5 h detected alterations in the hippocampal expression of 533 genes (Vecsey et al. 2012). A bioinformatics assessment pointed to a marked downregulation of translation through the insulin signaling pathway, including the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase with a major role in cell metabolism and protein synthesis (Wullschleger et al. 2006). Sleep deprivation decreased both the absolute and the phosphorylated levels of mTOR, with a return to basal levels of expression after a 2.5 h period of sleep. The result suggests that the physiological deficits caused by sleep deprivation are in part related to the impairment of protein synthesis mediated by mTOR.

There is also evidence that sleep deprivation increases the expression of molecular chaperones involved with the folding and oligomerization of newly synthesized proteins. For instance, brain expression of the binding immunoglobulin protein (BiP), also known as the 78-kDa glucose-regulated protein (GRP-78), is significantly upregulated by sleep deprivation in Drosophila (Shaw et al. 2000), birds, and rodents (Cirelli and Tononi 2000b; Shaw et al. 2000; Greenspan et al. 2001; Naidoo et al. 2005; Cirelli et al. 2006; Mackiewicz et al. 2007; Jones et al. 2008). Found in the endoplasmic reticulum, BiP is a chaperone that binds to newly synthesized proteins to facilitate their folding and oligomerization. The upregulation of BiP expression by sleep deprivation likely determines the upregulation of protein levels corresponding to a plethora of different genes.

7 Changes in Serum Protein Levels After Sleep Deprivation may Indirectly Reflect Changes in Gene Expression

Given the important influence of sleep on a great number of metabolic pathways, it is not surprising that sleep deprivation induces major metabolic disarray, including changes in serum protein levels. These may reflect changes in gene expression, but may also reflect changes in the release, degradation, and turnover of these molecules. The hormones, cytokines, and other proteins whose expression levels are affected include leptin, ghrelin, the thyroid hormones T3 and T4, interleukin 6 (IL-6), TNF-alpha, and C-reactive protein (CRP). Combined, changes in the levels of these proteins lead to energetic imbalance, impairment of the glucose metabolism, and metabolic syndrome (Mullington et al. 2009). In particular, REM sleep deprivation increases IL-1B, IL-6, and IL-12 (P70) serum levels, as well as the liver expression of IL-1B and IL-6 receptors in rodents (Gorczynski et al. 2005; Pandey and Kar 2011). These findings corroborate and greatly extend the earlier demonstration of a modulatory role of sleep on the expression of interleukin-1 beta

(IL-1B), an important pro-inflammatory cytokine (Mackiewicz et al. 1996). REM sleep deprivation also elevates the metabolic rate by increasing expression of the UCP1 gene, which encodes a protein involved in the dissipation of mitochondrial energy as heat, instead of ATP formation (Koban and Swinson 2005). An investigation of the effects of sleep deprivation on the inflammatory response in mice detected increased levels of IL-6 and IL-10 and decreased levels of TNF-alpha in animals treated with lipopolysaccharide (Weil et al. 2009).

In humans, one night of sleep loss leads to increased levels of IL-6 and TNF-alpha (Irwin et al. 2006). Chronic sleep loss for 1 week in young adults leads to increased levels of IL-6 in both males and females, while TNF-alpha is increased only in men (Vgontzas et al. 2004). Subjects with sleep limited to 4 h per night show increased levels of IL-6, in comparison with subjects sleeping 8 h per night; no significant differences between these groups were seen for TNF or CRP (Haack et al. 2007). Sleep restriction for 5 nights induces lymphocyte activation and upregulation of IL-1, IL-6, IL-17, and CRP (van Leeuwen et al. 2009). The studies of patients with obstructive sleep apnea are not conclusive: While some report increases, other find unchanged levels (Arnardottir et al. 2009). An investigation of 70 patients found that poor sleep is associated with higher concentrations of vascular endothelial growth factor (VEGF) and that fatigue-related reduction in activity is associated with increased TNF-alpha levels (Guess et al. 2009). Night-shift workers show increased levels of IL-6 and CRP, as well as elevated counts of white blood cells, neutrophils, lymphocytes, and platelets (Khosro et al. 2011). Overall, sleep deprivation is associated with a strong inflammatory response.

8 Sleep Deprivation and Genes Related to Cellular Stress Responses

Sleep loss stresses the organism as a whole, challenging its equilibrium at multiple levels, from the molecular and cellular domains to the complex interaction of entire systems, leading to behaviors such as anxiety, fear, aggressiveness, and helplessness. Autonomic responses and activation of the hypothalamus–pituitary–adrenal (HPA) axis (Herman and Cullinan 1997; Ziegler and Herman 2002), including enhanced glucocorticoid release, lead to the transcriptional upregulation of specific genes. The mRNA levels of the serum/glucocorticoid-induced serine/threonine kinase 1 (Sgk1), which activates ion channels in response to changes in cell hydration, are increased after 8 h of sleep deprivation, but not after spontaneous waking. Sleep deprivation was achieved by multimodal sensory stimulation, which consisted of the presentation of novel objects or odors, moving the animal to another cage and tapping the cage (Cirelli and Tononi 2000b). Another study found that Sgk1 mRNA levels are increased almost twofold in the dorsal raphe nucleus and more than twofold in the locus coeruleus in rats deprived of sleep for 24 h. In this case, sleep deprivation was performed by gently handling the animals, and differential analysis of gene expression was used to assess mRNA levels (Conti et al. 2007). More recently,

several stress-related genes including Sgk, the cyclin-dependent kinase inhibitor 1A (Cdkn1a), (BDNF), secretogranin II (Scg2), prokineticin 2 (Prok2), and the heat-shock 27-kDa protein 1 (Hspb1) were shown to be upregulated in animals kept awake for 6 h by multimodal sensory stimulation (including cage rotation). To assess gene expression, seven brain regions were submitted to laser microdissection, and main genes were selected through cDNA microarray for subsequent in situ hybridization confirmation (Thompson et al. 2010).

Sleep deprivation also affects the expression of genes related to stress in glial cells, such as the macrophage inhibitor factor-related protein 14 (MRP14), the heat-shock protein 27 (Hsp27), and the aB-crystallin (Cryab) (Cirelli et al. 2006). MRP14 is found in microglial cells (Postler et al. 1997; Staba et al. 2002), while Hsp27 and Cryab are heat-shock proteins with a protective role in oligodendrocytes and astrocytes (Goldbaum and Richter-Landsberg 2001). Altogether, these results point to the global reach of sleep deprivation, which negatively affects the organism as a whole, while at the same time stressing individual cells quite locally.

9 Sleep Deprivation, Gene Expression, and Cognition

Sleep deprivation affects the expression of immediate early genes, genes coding for neurotrophic factors, and various other genes that directly or indirectly affect neuronal plasticity, which in turn support brain function and cognitive processes. However, the finding that many of these genes are up-regulated after sleep deprivation seems at odds with the established fact that sleep deprivation causes impairments in cognitive function. The fact that plasticity factors involved with learning and memory (Guzowski et al. 2000; Jones et al. 2001; Bozon et al. 2003) are up-regulated by sleep deprivation poses a conundrum, given the evidence that sleep deprivation produces mnemonic impairment (Pearlman 1969; Graves et al. 2003; Seugnet et al. 2011; Havekes et al. 2012; Kumar and Jha 2012). One possible explanation for these results is the notion that learning triggers gene expression in specific subsets of neurons, while sleep deprivation affects neuronal populations in a generalized manner. Such a scenario is compatible with evidence that REM sleep triggers the upregulation of Zif-268 and Arc expression in the cerebral cortex and hippocampus of rats previously exposed to novel waking experience (Ribeiro et al. 1999, 2002, 2007; Ulloor and Datta 2005). This view is also supported by results showing that the detrimental effects of sleep deprivation on contextual fear conditioning are caused by a disruption of signaling via cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). Sleep deprivation for 5 h was followed by electrophysiological recordings and stimulation of hippocampal slices in mice with or without exposure to contextual fear conditioning. Two forms of long-term potentiation (LTP) dependent on cAMP and PKA were impaired by sleep deprivation, while LTP forms independent of cAMP/ PKA signaling remained unaltered. Sleep deprivation decreased CREB phosphorylation required for Zif-268 transcriptional regulation, seemingly at variance with several studies showing increased

Zif-268 expression after sleep deprivation (Sect. 4.2). Further experiments showed that inhibitors of cyclic nucleotide phosphodiesterases (PDE) rescued cAMP-dependent plasticity and cAMP levels in sleep-deprived mice. PDE-specific cAMP breakdown was enhanced in sleep-deprived mice, and in vivo PDE inhibition rescued the mnemonic deficit produced by sleep deprivation (Vecsey et al. 2009).

10 Conclusion

Sleep deprivation represents a major physiological challenge, with overarching consequences for the expression of genes related to metabolism, stress, cognition, and immunity. The large number of genes whose expression is affected by sleep deprivation reflects the great complexity of the genomic response triggered by sleep. The consequences of sleep deprivation include cognitive deficits, inflammation, general impairment of protein translation, metabolic imbalance, and thermal deregulation. While several diseases include sleep disturbances among their symptoms—including psychosis, depression, and Parkinson's and Alzheimer's disease—sleep loss per se is a risk factor for psychiatric and neurological diseases (Frank et al. 2013; Palma et al. 2013). A better understanding of the impact of sleep deprivation on gene expression shall provide meaningful insights into both basic and applied scientific questions. It should also help mitigate the cognitive and health problems faced by those that suffer from sleep loss due to professional schedules and/or family responsibilities.

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References

Aldabal L, Bahammam AS (2011) Metabolic, endocrine, and immune consequences of sleep deprivation. Open Respir Med J 5:31–43

Alkadhi K, Zagaar M, Alhaider I, Salim S, Aleisa A (2013) Neurobiological consequences of sleep deprivation. Curr Neuropharmacol 11(3):231–249

Appelbaum L, Wang G, Yokogawa T, Skariah GM, Smith SJ, Mourrain P, Mignot E (2010) Circadian and homeostatic regulation of structural synaptic plasticity in hypocretin neurons. Neuron 68(1):87–98

Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI (2009) Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep 32(4):447–470

Aydin A, Selvi Y, Besiroglu L, Boysan M, Atli A, Ozdemir O, Kilic S, Balaharoglu R (2013) Mood and metabolic consequences of sleep deprivation as a potential endophenotype' in bipolar disorder. J Affect Disord 150(2):284–294

Barf RP, Desprez T, Meerlo P, Scheurink AJ (2012) Increased food intake and changes in metabolic hormones in response to chronic sleep restriction alternated with short periods of sleep allowance. Am J Physiol Regul Integr Comp Physiol 302(1):R112–R117

Bergmann BM, Everson CA, Kushida CA, Fang VS, Leitch CA, Schoeller DA, Refetoff S, Rechtschaffen A (1989a) Sleep deprivation in the rat: V. Energy use and mediation. Sleep 12 (1):31–41

Bergmann BM, Kushida CA, Everson CA, Gilliland MA, Obermeyer W, Rechtschaffen A (1989b) Sleep deprivation in the rat: II. Methodology. Sleep 12(1):5–12

Bevins RA, Klebaur JE, Bardo MT (1997) Individual differences in response to novelty, amphetamine-induced activity and drug discrimination in rats. Behav Pharmacol 8(2–3):113–123

Boyd JG, Gordon T (2003a) Glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor sustain the axonal regeneration of chronically axotomized motoneurons in vivo. Exp Neurol 183(2):610–619

Boyd JG, Gordon T (2003b) Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. Mol Neurobiol 27(3):277–324

Bozon B, Kelly A, Josselyn SA, Silva AJ, Davis S, Laroche S (2003) MAPK, CREB and zif268 are all required for the consolidation of recognition memory. Philos Trans R Soc Lond B Biol Sci 358(1432):805–814

Bramham CR, Alme MN, Bittins M, Kuipers SD, Nair RR, Pai B, Panja D, Schubert M, Soule J, Tiron A, Wibrand K (2010) The Arc of synaptic memory. Exp Brain Res 200(2):125–140

Brandt JA, Churchill L, Guan Z, Fang J, Chen L, Krueger JM (2001) Sleep deprivation but not a whisker trim increases nerve growth factor within barrel cortical neurons. Brain Res 898 (1):105–112

Bustin SA, Benes V, Nolan T, Pfaffl MW (2005) Quantitative real-time RT-PCR–a—perspective. J Mol Endocrinol 34(3):597–601

Calegare BFA, Fernandes L, Tufik S, D'Almeida V (2010) Biochemical, biometrical and behavioral changes in male offspring of sleep-deprived mice. Psychoneuroendocrinology 35 (5):775–784

Christy B, Nathans D (1989) DNA binding site of the growth factor-inducible protein Zif268. Proc Natl Acad Sci USA 86(22):8737–8741

Cirelli C (2002) How sleep deprivation affects gene expression in the brain: a review of recent findings. J Appl Physiol 92(1):394–400

Cirelli C (2006) Cellular consequences of sleep deprivation in the brain☆. Sleep Med Rev 10 (5):307–321

Cirelli C, Tononi G (2000a) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. J Neurosci 20(24):9187–9194

Cirelli C, Tononi G (2000b) Gene expression in the brain across the sleep-waking cycle. Brain Res 885(2):303–321

Cirelli C, Tononi G (2000c) On the functional significance of c-fos induction during the sleep-waking cycle. Sleep 23(4):453–469

Cirelli C, Pompeiano M, Tononi G (1995) Sleep deprivation and c-fos expression in the rat brain. J Sleep Res 4:92–106

Cirelli C, Pompeiano M, Tononi G (1996) Neuronal gene expression in the waking state: a role for the locus coeruleus. Science 274(5290):1211–1215

Cirelli C, LaVaute TM, Tononi G (2005) Sleep and wakefulness modulate gene expression in Drosophila. J Neurochem 94(5):1411–1419

Cirelli C, Faraguna U, Tononi G (2006) Changes in brain gene expression after long-term sleep deprivation. J Neurochem 98(5):1632–1645

Clinton SM, Bedrosian TA, Abraham AD, Watson SJ, Akil H (2010) Neural and environmental factors impacting maternal behavior differences in high- versus low-novelty-seeking rats. Horm Behav 57(4–5):463–473

Conti B, Maier R, Barr AM, Morale MC, Lu X, Sanna PP, Bilbe G, Hoyer D, Bartfai T (2007) Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. Mol Psychiatry 12(2):167–189

Dellu F, Piazza PV, Mayo W, Le Moal M, Simon H (1996) Novelty-seeking in rats–biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. Neuropsychobiology 34(3):136–145

Duclot F, Hollis F, Darcy MJ, Kabbaj M (2011) Individual differences in novelty-seeking behavior in rats as a model for psychosocial stress-related mood disorders. Physiol Behav 104(2):296–305

Ennaceur A, Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. Behav Brain Res 31(1):47–59

Everson CA (1995) Functional consequences of sustained sleep deprivation in the rat. Behav Brain Res 69(1–2):43–54

Everson CA, Smith CB, Sokoloff L (1994) Effects of prolonged sleep deprivation on local rates of cerebral energy metabolism in freely moving rats. J Neurosci 14(11 Pt 2):6769–6778

Filipowicz W, Bhattacharyya SN, Sonenberg N (2008) Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet 9(2):102–114

Frank MG (2012) Sleep and brain activity. Academic Press, New York

Frank E, Sidor MM, Gamble KL, Cirelli C, Sharkey KM, Hoyle N, Tikotzky L, Talbot LS, McCarthy MJ, Hasler BP (2013) Circadian clocks, brain function, and development. Ann N Y Acad Sci 1306:43–67

Franken P, Dijk DJ, Tobler I, Borbely AA (1991) Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. Am J Physiol 261(1 Pt 2):R198–R208

Freeman WM, Robertson DJ, Vrana KE (2000) Fundamentals of DNA hybridization arrays for gene expression analysis. Biotechniques 29(5):1042–1046, 1048–1055

Fujihara H, Sei H, Morita Y, Ueta Y, Morita K (2003) Short-term sleep disturbance enhances brain-derived neurotrophic factor gene expression in rat hippocampus by acting as internal stressor. J Mol Neurosci 21(3):223–232

Gall JG, Pardue ML (1969) Formation and detection of RNA-DNA hybrid molecules in cytological preparations. Proc Natl Acad Sci USA 63(2):378–383

Gallagher S, Winston SE, Fuller SA, Hurrell JG (2004) Immunoblotting and immunodetection. Curr Protoc Neurosci (Chapter 5:Unit 5) 19

Ghosh A, Carnahan J, Greenberg ME (1994) Requirement for BDNF in activity-dependent survival of cortical neurons. Science 263(5153):1618–1623

Goldbaum O, Richter-Landsberg C (2001) Stress proteins in oligodendrocytes: differential effects of heat shock and oxidative stress. J Neurochem 78(6):1233–1242

Gonnissen HK, Adam TC, Hursel R, Rutters F, Verhoef SP, Westerterp-Plantenga MS (2013) Sleep duration, sleep quality and body weight: parallel developments. Physiol Behav 121:112–116

Gorczynski RM, Gorczynski CP, Gorczynski LY, Hu J, Lu J, Manuel J, Lee L (2005) Neutral buoyancy and sleep-deprived serum factors alter expression of cytokines regulating osteogenesis. Acta Astronautica 56(9–12):890–899

Graves LA, Heller EA, Pack AI, Abel T (2003) Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. Learn Mem 10:168–176

Green S, Chambon P (1988) Nuclear receptors enhance our understanding of transcription regulation. Trends Genet 4(11):309–314

Greenspan RJ, Tononi G, Cirelli C, Shaw PJ (2001) Sleep and the fruit fly. Trends Neurosci 24 (3):142–145

Guess J, Burch JB, Ogoussan K, Armstead CA, Hongmei Z, Wagner S, Hebert JR, Wood P, Youngstedt SD, Hofseth LJ, Singh UP, Dawen X, Hrushesky WJM (2009) Circadian Disruption, Per3, and Human Cytokine Secretion. Integr Cancer Ther 8(4):329–336

Guindalini C, Andersen ML, Alvarenga T, Lee K, Tufik S (2009) To what extent is sleep rebound effective in reversing the effects of paradoxical sleep deprivation on gene expression in the brain? Behav Brain Res 201(1):53–58

Guzman-Marin R, Suntsova N, Stewart DR, Gong H, Szymusiak R, McGinty D (2003) Sleep deprivation reduces proliferation of cells in the dentate gyrus of the hippocampus in rats. J Physiol 549(Pt 2):563–571

Guzman-Marin R, Suntsova N, Methippara M, Greiffenstein R, Szymusiak R, McGinty D (2005) Sleep deprivation suppresses neurogenesis in the adult hippocampus of rats. Eur J Neurosci 22 (8):2111–2116

Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol 575(Pt 3):807–819

Guzowski JF, Lyford GL, Stevenson GD, Houston FP, McGaugh JL, Worley PF, Barnes CA (2000) Inhibition of activity-dependent arc protein expression in the rat hippocampus impairs the maintenance of long-term potentiation and the consolidation of long-term memory. J Neurosci 20(11):3993–4001

Haack M, Sanchez E, Mullington JM (2007) Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep 30(9):1145–1152

Hagewoud R, Havekes R, Novati A, Keijser JN, Van der Zee EA, Meerlo P (2010a) Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. J Sleep Res 19(2):280–288

Hagewoud R, Havekes R, Tiba PA, Novati A, Hogenelst K, Weinreder P, Van der Zee EA, Meerlo P (2010b) Coping with sleep deprivation: shifts in regional brain activity and learning strategy. Sleep 33(11):1465–1473

Hagewoud R, Whitcomb SN, Heeringa AN, Havekes R, Koolhaas JM, Meerlo P (2010c) A time for learning and a time for sleep: the effect of sleep deprivation on contextual fear conditioning at different times of the day. Sleep 33(10):1315–1322

Hairston IS (2004) Sleep deprivation effects on growth factor expression in neonatal rats: a potential role for bdnf in the mediation of delta power. J Neurophysiol 91(4):1586–1595

Hamatake M, Miyazaki N, Sudo K, Matsuda M, Sadakata T, Furuya A, Ichisaka S, Hata Y, Nakagawa C, Nagata K, Furuichi T, Katoh-Semba R (2011) Phase advance of the light-dark cycle perturbs diurnal rhythms of brain-derived neurotrophic factor and neurotrophin-3 protein levels, which reduces synaptophysin-positive presynaptic terminals in the cortex of juvenile rats. J Biol Chem 286(24):21478–21487

Havekes R, Vecsey CG, Abel T (2012) The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. Cell Signal 24(6):1251–1260

Hawk J, Abel T (2010) Role of gene transcription in long-term memory storage. In: George FK, Michel Le M, Richard MLM, ThompsonA2, George F. Koob, Richard FT (eds) Encyclopedia of behavioral neuroscience. Academic Press, Oxford, pp 161–179

Hawk JD, Abel T (2011) The role of NR4A transcription factors in memory formation. Brain Res Bull 85(1–2):21–29

Henderson ND (1970) Behavioral reactions of Wistar rats to conditioned fear stimuli, novelty, and noxious stimulation. J Psychol 75(2d Half):19–34

Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 20(2):78–84

Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S (2006) Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med 166(16):1756–1762

Jin L, Lloyd RV (1997) In situ hybridization: methods and applications. J Clin Lab Anal 11(1):2–9

Jones MW, Errington ML, French PJ, Fine A, Bliss TV, Garel S, Charnay P, Bozon B, Laroche S, Davis S (2001) A requirement for the immediate early gene Zif268 in the expression of late LTP and long-term memories. Nat Neurosci 4(3):289–296

Jones S, Pfister-Genskow M, Benca RM, Cirelli C (2008) Molecular correlates of sleep and wakefulness in the brain of the white-crowned sparrow. J Neurochem 105(1):46–62

Jouvet M (1967) The states of sleep. Sci Am 216(2):62–68

Jouvet M (1994) Paradoxical sleep mechanisms. Sleep 17(8 Suppl.):S77–S83

Jouvet D, Vimont P, Delorme F, Jouvet M (1964) Study of selective deprivation of the paradoxal sleep phase in the cat. C R Seances Soc Biol Fil 158:756–759

Kabbaj M, Akil H (2001) Individual differences in novelty-seeking behavior in rats: a c-fos study. Neuroscience 106(3):535–545

Kayser MS, Yue Z, Sehgal A (2014) A critical period of sleep for development of courtship circuitry and behavior in Drosophila. Science 344(6181):269–274

Khosro S, Alireza S, Omid A, Forough S (2011) Night work and inflammatory markers. Indian J Occup Environ Med 15(1):38–41

Killick R, Banks S, Liu PY (2012) Implications of sleep restriction and recovery on metabolic outcomes. J Clin Endocrinol Metab 97(11):3876–3890

Knapska E, Kaczmarek L (2004) A gene for neuronal plasticity in the mammalian brain: Zif268/Egr-1/NGFI-A/Krox-24/TIS8/ZENK? Prog Neurobiol 74(4):183–211

Knutson KL, Spiegel K, Penev P, Van Cauter E (2007) The metabolic consequences of sleep deprivation. Sleep Med Rev 11(3):163–178

Koban M, Swinson KL (2005) Chronic REM-sleep deprivation of rats elevates metabolic rate and increases UCP1 gene expression in brown adipose tissue. Am J Physiol Endocrinol Metab 289 (1):E68–E74

Kovacs KJ (1998) c-Fos as a transcription factor: a stressful (re)view from a functional map. Neurochem Int 33(4):287–297

Kumar T, Jha SK (2012) Sleep deprivation impairs consolidation of cued fear memory in rats. PLoS One 7(10):e47042

Kushida CA, Bergmann BM, Rechtschaffen A (1989) Sleep deprivation in the rat: IV. Paradoxical sleep deprivation. Sleep 12(1):22–30

Kushikata T, Kubota T, Fang J, Krueger JM (2003) Neurotrophins 3 and 4 enhance non-rapid eye movement sleep in rabbits. Neurosci Lett 346(3):161–164

Landis CA, Collins BJ, Cribbs LL, Sukhatme VP, Bergmann BM, Rechtschaffen A, Smalheiser NR (1993) Expression of Egr-1 in the brain of sleep deprived rats. Brain Res Mol Brain Res 17 (3–4):300–306

Ledoux L, Sastre JP, Buda C, Luppi PH, Jouvet M (1996) Alterations in c-fos expression after different experimental procedures of sleep deprivation in the cat. Brain Res 735(1):108–118

Lipsky RH, Marini AM (2007) Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. Ann N Y Acad Sci 1122:130–143

Lyford GL, Yamagata K, Kaufmann WE, Barnes CA, Sanders LK, Copeland NG, Gilbert DJ, Jenkins NA, Lanahan AA, Worley PF (1995) Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. Neuron 145(2):433–434

Maas S (2010) Gene regulation through RNA editing. Discov Med 10(54):379–386

Mackiewicz M, Sollars PJ, Ogilvie MD, Pack AI (1996) Modulation of IL-1 beta gene expression in the rat CNS during sleep deprivation. Neuroreport 7(2):529–533

Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI (2007) Macromolecule biosynthesis: a key function of sleep. Physiol Genomics 31(3):441–457

Mackiewicz M, Naidoo N, Zimmerman JE, Pack AI (2008) Molecular Mechanisms of Sleep and Wakefulness. Ann N Y Acad Sci 1129(1):335–349

Maloney KJ, Mainville L, Jones BE (2002) c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. Eur J Neurosci 15(4):774–778

Maret S, Dorsaz S, Gurcel L, Pradervand S, Petit B, Pfister C, Hagenbuchle O, O'Hara BF, Franken P, Tafti M (2007) Homer1a is a core brain molecular correlate of sleep loss. Proc Natl Acad Sci USA 104(50):20090–20095

Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright Jr KP (2013) Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. Proc Natl Acad Sci USA 110(14):5695–5700

Maxwell MA, Muscat GE (2006) The NR4A subgroup: immediate early response genes with pleiotropic physiological roles. Nucl Recept Signal 4:e002

McKenna NJ, O'Malley BW (2002) Combinatorial control of gene expression by nuclear receptors and coregulators. Cell 108(4):465–474

McManus CJ, Graveley BR (2011) RNA structure and the mechanisms of alternative splicing. Curr Opin Genet Dev 21(4):373–379

Mendelson WB, Guthrie RD, Frederick G, Wyatt RJ (1974) The flower pot technique of rapid eye movement (REM) sleep deprivation. Pharmacol Biochem Behav 2(4):553–556

Moller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R, Lo JC, Santhi N, von Schantz M, Smith CP, Dijk DJ (2013) Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. Proc Natl Acad Sci USA 110(12): E1132–E1141

Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK (2009) Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Prog Cardiovasc Dis 51 (4):294–302

Naidoo N, Giang W, Galante RJ, Pack AI (2005) Sleep deprivation induces the unfolded protein response in mouse cerebral cortex. J Neurochem 92(5):1150–1157

National Research Council of the National Academies (2003) Guidelines for the care and use of mammals in neuroscience and behavioral research. The National Academies Press, Washington

Nelson SE, Duricka DL, Campbell K, Churchill L, Krueger JM (2004) Homer1a and 1bc levels in the rat somatosensory cortex vary with the time of day and sleep loss. Neurosci Lett 367 (1):105–108

Nitabach MN, Mongrain V, La Spada F, Curie T, Franken P (2011) Sleep loss reduces the DNA-binding of BMAL1, clock, and NPAS2 to specific clock genes in the mouse cerebral cortex. PLoS One 6(10):e26622

Ocampo-Garces A, Molina E, Rodriguez A, Vivaldi EA (2000) Homeostasis of REM sleep after total and selective sleep deprivation in the rat. J Neurophysiol 84(5):2699–2702

O'Hara BF, Young KA, Watson FL, Heller HC, Kilduff TS (1993) Immediate early gene expression in brain during sleep deprivation: preliminary observations. Sleep 16(1):1–7

Okuno H, Akashi K, Ishii Y, Yagishita-Kyo N, Suzuki K, Nonaka M, Kawashima T, Fujii H, Takemoto-Kimura S, Abe M, Natsume R, Chowdhury S, Sakimura K, Worley PF, Bito H (2012) Inverse synaptic tagging of inactive synapses via dynamic interaction of Arc/Arg3.1 with CaMKIIbeta. Cell 149(4):886–898

Palma JA, Urrestarazu E, Iriarte J (2013) Sleep loss as risk factor for neurologic disorders: a review. Sleep Med 14(3):229–236

Pandey AK, Kar SK (2011) REM sleep deprivation of rats induces acute phase response in liver. Biochem Biophys Res Commun 410(2):242–246

Pearlman CA (1969) Effect of rapid eye movement (dreaming) sleep deprivation on retention of avoidance learning in rats. Rep US Naval Submarine Med Cent 22(1):1–4

Pellegrino R, Sunaga DY, Guindalini C, Martins RC, Mazzotti DR, Wei Z, Daye ZJ, Andersen ML, Tufik S (2012) Whole blood genome-wide gene expression profile in males after prolonged wakefulness and sleep recovery. Physiol Genomics 44(21):1003–1012

Pisula W, Siegel J (2005) Exploratory behavior as a function of environmental novelty and complexity in male and female rats. Psychol Rep 97(2):631–638

Pompeiano M, Cirelli C, Tononi G (1992) Effects of sleep deprivation on fos-like immunoreactivity in the rat brain. Arch Ital Biol 130(4):325–335

Pompeiano M, Cirelli C, Tononi G (1994) Immediate-early genes in spontaneous wakefulness and sleep: expression of c-fos and NGIF-A mRNA and protein. J Sleep Res 3:80–96

Pompeiano M, Cirelli C, Ronca-Testoni S, Tononi G (1997) NGFI-A expression in the rat brain after sleep deprivation. Brain Res Mol Brain Res 46(1–2):143–153

Postler E, Lehr A, Schluesener H, Meyermann R (1997) Expression of the S-100 proteins MRP-8 and -14 in ischemic brain lesions. Glia 19(1):27–34

Ramon F, Mendoza-Angeles K, Hernandez-Falcon J (2012) Sleep in invertebrates: crayfish. Front Biosci (Schol Ed) 4:1190–1200

Rechtschaffen A, Bergmann BM (1995) Sleep deprivation in the rat by the disk-over-water method. Behav Brain Res 69(1–2):55–63

Rechtschaffen A, Gilliland MA, Bergmann BM, Winter JB (1983) Physiological correlates of prolonged sleep deprivation in rats. Science 221(4606):182–184
Rechtschaffen A, Bergmann BM, Gilliland MA, Bauer K (1999) Effects of method, duration, and sleep stage on rebounds from sleep deprivation in the rat. Sleep 22(1):11–31
Ribeiro S, Goyal V, Mello CV, Pavlides C (1999) Brain gene expression during REM sleep depends on prior waking experience. Learn Mem 6(5):500–508
Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye- movement sleep. J Neurosci 22(24):10914–10923
Ribeiro S, Shi X, Engelhard M, Zhou Y, Zhang H, Gervasoni D, Lin SC, Wada K, Lemos NAM, Nicolelis MAL (2007) Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. Front Neurosci 1(1):43–55
Roman V, Walstra I, Luiten PG, Meerlo P (2005) Too little sleep gradually desensitizes the serotonin 1A receptor system. Sleep 28(12):1505–1510
Sei H, Saitoh D, Yamamoto K, Morita K, Morita Y (2000) Differential effect of short-term REM sleep deprivation on NGF and BDNF protein levels in the rat brain. Brain Res 877(2):387–390
Seugnet L, Suzuki Y, Donlea JM, Gottschalk L, Shaw PJ (2011) Sleep deprivation during early-adult development results in long-lasting learning deficits in adult Drosophila. Sleep 34 (2):137–146
Shaw PJ, Cirelli C, Greenspan RJ, Tononi G (2000) Correlates of sleep and waking in Drosophila melanogaster. Science 287(5459):1834–1837
Shiao YH (2003) A new reverse transcription-polymerase chain reaction method for accurate quantification. BMC Biotechnol 3:22
Shiraishi-Yamaguchi Y, Furuichi T (2007) The Homer family proteins. Genome Biol 8(2):206
Smith C, Kelly G (1988) Paradoxical sleep deprivation applied two days after end of training retards learning. Physiol Behav 43(2):213–216
Sossin WS, Barker PA (2007) Something old, something new: BDNF-induced neuron survival requires TRPC channel function. Nat Neurosci 10(5):537–538
Staba RJ, Wilson CL, Fried I, Engel J Jr (2002) Single neuron burst firing in the human hippocampus during sleep. Hippocampus 12(6):724–734
Taishi P, Sanchez C, Wang Y, Fang J, Harding JW, Krueger JM (2001) Conditions that affect sleep alter the expression of molecules associated with synaptic plasticity. Am J Physiol Regul Integr Comp Physiol 281(3):R839–R845
Terao A, Greco MA, Davis RW, Heller HC, Kilduff TS (2003) Region-specific changes in immediate early gene expression in response to sleep deprivation and recovery sleep in the mouse brain. Neuroscience 120(4):1115–1124
Terao A, Wisor JP, Peyron C, Apte-Deshpande A, Wurts SW, Edgar DM, Kilduff TS (2006) Gene expression in the rat brain during sleep deprivation and recovery sleep: an Affymetrix GeneChip® study. Neuroscience 137(2):593–605
Thompson CL, Wisor JP, Lee C-K, Pathak SD, Gerashchenko D, Smith KA, Fischer SR, Kuan CL, Sunkin SM, Ng LL, Lau C, Hawrylycz M, Jones AR, Kilduff TS, Lein ES (2010) Molecular and anatomical signatures of sleep deprivation in the mouse brain. Front Neurosci 4:165. doi: 10.3389/fnins.2010.00165
Thor DH, Harrison RJ, Schneider SR, Carr WJ (1988) Sex differences in investigatory and grooming behaviors of laboratory rats (Rattus norvegicus) following exposure to novelty. J Comp Psychol 102(2):188–192
Tischmeyer W, Grimm R (1999) Activation of immediate early genes and memory formation. Cell Mol Life Sci 55(4):564–574
Tononi G, Cirelli C (2001) Modulation of brain gene expression during sleep and wakefulness: a review of recent findings. Neuropsychopharmacology 25(5 Suppl):S28–S35
Tononi G, Pompeiano M, Cirelli C (1994) The locus coeruleus and immediate-early genes in spontaneous and forced wakefulness. Brain Res Bull 35(5–6):589–596

Tu JC, Xiao B, Yuan JP, Lanahan AA, Leoffert K, Li M, Linden DJ, Worley PF (1998) Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. Neuron 21(4):717–726

Tufik S, Andersen ML, Bittencourt LR, Mello MT (2009) Paradoxical sleep deprivation: neurochemical, hormonal and behavioral alterations. Evidence from 30 years of research. An Acad Bras Cienc 81(3):521–538

Ulloor J, Datta S (2005) Spatio-temporal activation of cyclic AMP response element-binding protein, activity-regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. J. Neurochem. 95(2):418–428

van der Borght K, Ferrari F, Klauke K, Roman V, Havekes R, Sgoifo A, van der Zee EA, Meerlo P (2006) Hippocampal cell proliferation across the day: increase by running wheel activity, but no effect of sleep and wakefulness. Behav Brain Res 167(1):36–41

van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, Sallinen M, Harma M, Porkka-Heiskanen T, Alenius H (2009) Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One 4(2):e4589

van Swinderen B (2007) 1.28—Sleep in invertebrates. Evolution of nervous systems. HK Editor-in-Chief: Jon. Academic Press, Oxford, p 451–456

Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li XY, Descalzi G, Kim SS, Chen T, Shang YZ, Zhuo M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. Nature 461(7267):1122–1125

Vecsey CG, Peixoto L, Choi JH, Wimmer M, Jaganath D, Hernandez PJ, Blackwell J, Meda K, Park AJ, Hannenhalli S, Abel T (2012) Genomic analysis of sleep deprivation reveals translational regulation in the hippocampus. Physiol Genomics 44(20):981–991

Ventimiglia R, Mather PE, Jones BE, Lindsay RM (1995) The neurotrodhins BDNF, NT-3 and NT-4/5 promote survival and morphological and biochemical differentiation of striatal neurons In Vitro. Eur J Neurosci 7(2):213–222

Ventskovska O, Porkka-Heiskanen T, Karpova NN (2014) Spontaneous sleep-wake cycle and sleep deprivation differently induce Bdnf1, Bdnf4 and Bdnf9a DNA methylation and transcripts levels in the basal forebrain and frontal cortex in rats. J Sleep Res

Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP (2004) Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 89(5):2119–2126

Vivaldi EA, Bassi A, Estrada J, Garrido I, Diaz J, Ocampo-Garces A (2008) On-line analysis of biosignals for the automation of total and specific sleep deprivation in the rat. Biol Res 41 (4):439–452

Vogel C, Marcotte EM (2012) Insights into the regulation of protein abundance from proteomic and transcriptomic analyses. Nat Rev Genet 13(4):227–232

Wallingford JK, Deurveilher S, Currie RW, Fawcett JP, Semba K (2014) Increases in mature brain-derived neurotrophic factor protein in the frontal cortex and basal forebrain during chronic sleep restriction in rats: possible role in initiating allostatic adaptation. Neuroscience 277:174–183

Wang H, Liu Y, Briesemann M, Yan J (2010) Computational analysis of gene regulation in animal sleep deprivation. Physiol Genomics 42(3):427–436

Weil ZM, Norman GJ, Karelina K, Morris JS, Barker JM, Su AJ, Walton JC, Bohinc S, Nelson RJ, DeVries AC (2009) Sleep deprivation attenuates inflammatory responses and ischemic cell death. Exp Neurol 218(1):129–136

Wu RS, Huang CC, Pan CH, Wu KC, Chen CC, Liu SK, Tang CL, Wu CH (2011) Total sleep deprivation augments balloon angioplasty-induced neointimal hyperplasia in rats. Exp Physiol 96(11):1239–1247

Wullschleger S, Loewith R, Hall MN (2006) TOR signaling in growth and metabolism. Cell 124 (3):471–484

Xu A, Sakurai E, Kuramasu A, Zhang J, Li J, Okamura N, Zhang D, Yoshikawa T, Watanabe T, Yanai K (2010) Roles of hypothalamic subgroup histamine and orexin neurons on behavioral responses to sleep deprivation induced by the treadmill method in adolescent rats. J Pharmacol Sci 114(4):444–453

Youngblood BD, Zhou J, Smagin GN, Ryan DH, Harris RB (1997) Sleep deprivation by the "flower pot" technique and spatial reference memory. Physiol Behav 61(2):249–256

Ziegler DR, Herman JP (2002) Neurocircuitry of stress integration: anatomical pathways regulating the hypothalamo-pituitary-adrenocortical axis of the rat. Integr Comp Biol 42 (3):541–551

Zielinski MR, Kim Y, Karpova SA, McCarley RW, Strecker RE, Gerashchenko D (2014) Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression. Neurosci Lett 580:27–31

Zimmerman JE, Rizzo W, Shockley KR, Raizen DM, Naidoo N, Mackiewicz M, Churchill GA, Pack AI (2006) Multiple mechanisms limit the duration of wakefulness in Drosophila brain. Physiol Genomics 27(3):337–350

Sleep and Synaptic Homeostasis

Vladyslav V. Vyazovskiy and Ugo Faraguna

Abstract In the last decades a substantial knowledge about sleep mechanisms has been accumulated. However, the function of sleep still remains elusive. The difficulty with unraveling sleep's function may arise from the lack of understanding of how the multitude of processes associated with waking and sleep—from gene expression and single neuron activity to the whole brain dynamics and behavior—functionally and mechanistically relate to each other. Therefore, novel conceptual frameworks, which integrate and take into account the variety of phenomena occurring during waking and sleep at different levels, will likely lead to advances in our understanding of the function of sleep, above and beyond what merely descriptive or correlative approaches can provide. One such framework, the synaptic homeostasis hypothesis, focuses on wake- and sleep-dependent changes in synaptic strength. The core claim of this hypothesis is that learning and experience during wakefulness are associated with a net increase in synaptic strength. In turn, the proposed function of sleep is to provide synaptic renormalization, which has important implications with respect to energy needs, intracranial space, metabolic supplies, and, importantly, enables further plastic changes. In this article we review the empirical evidence for this hypothesis, which was obtained at several levels—from gene expression and cellular excitability to structural synaptic modifications and behavioral outcomes. We conclude that although the mechanisms behind the proposed role of sleep in synaptic homeostasis are undoubtedly complex, this conceptual framework offers a unique opportunity to provide mechanistic and functional explanation for many previously disparate observations, and define future research strategies.

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Contents

1 Introduction

Sleep has been defined as a reversible behavioral state, during which the sensory input is reduced, coordinated behavior is abolished, and cognitive activities are suspended (Borbely and Tononi 1998). Importantly, sleep is not only a state but is also a process, as it is manifested in specific patterns of brain activity that unfold in time and space in a highly complex manner. Despite several attempts to answer the fundamental question about the function(s) of sleep, why we sleep remains a mystery. In the last decades, many hypotheses for the function of sleep have been proposed, focusing on the maintenance of cellular energy homeostasis, synaptic plasticity, memory consolidation, thermoregulation, macromolecule biosynthesis, and others (Abel et al. 2013; Cirelli and Tononi 2008; Diekelmann and Born 2010; Frank 2006; Mackiewicz et al. 2007; Mignot 2008; Varshavsky 2012; Vyazovskiy and Harris 2013). These hypotheses are not mutually exclusive, and it is possible that sleep enables a variety of processes at the level of molecules, synapses, single neurons (and other cells), small and large neural networks, or the whole organism to occur in parallel. This chapter will address one specific hypothesis, known as the Synaptic Homeostasis Hypothesis (SHY), proposed by Tononi and Cirelli (2003, 2006, 2014). The SHY reconciles a multitude of empirical observations in a coherent framework, and bridges the gap between phenomena occurring at the level of individual synapses, the whole brain dynamics and behavioral performance.

2 Electrical Activity of the Awake and Sleeping Brain

The activity of the brain in mammals shows continuous fluctuations at multiple temporal and spatial scales, and it is tightly linked to vigilance states, movement, behavior and sensory processing (Nir et al. 2013; Petersen et al. 2003; Sakata and Harris 2009; Steriade et al. 2001; Vyazovskiy 2013; Vyazovskiy et al. 2009b; Vyazovskiy and Tobler 2012). Above all, on a timescale of minutes to hours the brain fluctuates regularly between two distinct states: wakefulness and sleep, which is of two kinds: non-rapid eye movement (NREM) sleep and REM sleep. A fundamental difference in brain activity defining wakefulness versus sleep arises from the necessity to engage in the acquisition and processing of information from the environment. Brain activity during awake states is largely regulated by ascending activating influences from specific subcortical waking-promoting areas (Brown et al. 2012; Jones 2005) and ongoing behavior (Petersen et al. 2003; Vyazovskiy et al. 2006). This is reflected in the wake electroencephalogram (EEG), which is distinguished from sleep by the absence of slow waves ($\sim$0.1–4 Hz) and, in rodents, by pronounced theta activity ($\sim$6–9 Hz) presumably arising from the hippocampus (Green and Arduini 1954; Sirota et al. 2008) (Fig. 1).

Conversely, cortical activity during NREM sleep is generally slower compared to both wakefulness and REM sleep (Hobson and McCarley 1971; Steriade et al. 2001; Vyazovskiy et al. 2004b, 2009b). Early studies showed that, upon falling asleep, the quasi-independent firing of neurons typical of the awake state is replaced by regular synchronous bursts of action potentials (Noda and Adey 1970; Verzeano and Negishi 1960). In more recent studies, intracellular single-cell recordings have shown that, during NREM sleep, virtually all cortical neurons engage in the so-called slow (<1 Hz) oscillation, consisting of a depolarized up state, when neurons show sustained firing, and a hyperpolarized down state, characterized by neuronal silence (Destexhe et al. 1999; Steriade et al. 1993c). During the up state, both pyramidal cells and interneurons are active, and excitation and inhibition are balanced at the synaptic level (Haider et al. 2006; Okun and Lampl 2008). Simultaneous EEG and intracellular or extracellular recordings have shown that slow waves are associated with transitions between up and down states or on and off periods in large populations of cortical neurons (Ji and Wilson 2007; Steriade et al. 2001), and high amplitude slow waves are associated with longer periods of neuronal silence (Fig. 2) and tighter synchrony at on–off and off–on transitions (Vyazovskiy and Harris 2013; Vyazovskiy et al. 2009b).

Surprisingly, 20 years after the slow oscillation was first described in the seminal triad of papers by Steriade et al. (1993a, b, c), its functional role remains unclear. At the macroscopic EEG level, the cellular slow oscillation is reflected in the Slow Wave Activity (SWA, EEG power between 0.5 and 4.0 Hz) during NREM sleep (Borbely 1982), which is the best characterized physiological marker of sleep intensity. One of the main defining features of sleep is that it is homeostatically

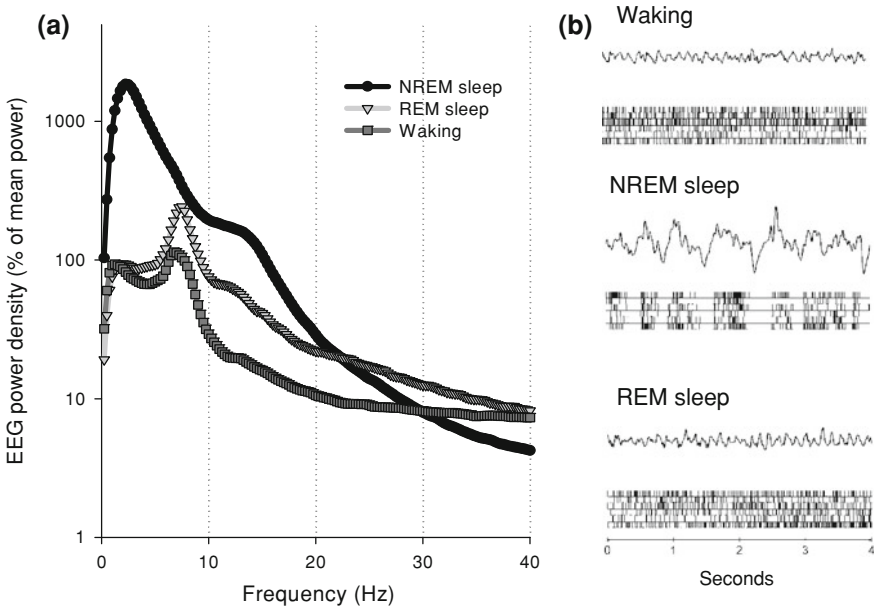

Fig. 1 **a** Twenty four hour EEG power spectra in NREM sleep, REM sleep and waking in one representative adult male rat (Wistar Kyoto strain). **b** EEG signals and corresponding cortical multiunit activity (raster plots below; each bar is a spike) representative of the three vigilance states. Note the fast irregular pattern of cortical firing in waking and REM sleep, and regular occurrence of generalized neuronal silence, corresponding to EEG slow waves, in NREM sleep

regulated (Cirelli and Tononi 2008; Tobler 2005). The main postulate of sleep homeostasis is "the longer we are active (and, perhaps, the more we are active), the deeper our subsequent sleep" (Daan et al. 1984). In other words, this implies that sleep need (or "sleep pressure") increases in proportion to the preceding duration of waking, and then dissipates during the ensuing sleep in proportion to its duration and intensity. In mammals and birds, sleep SWA is high in early sleep and decreases progressively within sleep to reach low levels several hours later (Jones et al. 2008; Tobler and Borbely 1986). This dynamics of sleep slow wave activity suggests that sleep is associated with a recovery process. However, neither the nature of the putative recovery processes, nor its relationship with the homeostatic changes in SWA are clear (Vyazovskiy and Harris 2013).

3 Global and Local Sleep Regulation

The first and perhaps most essential question that needs to be addressed is, what is "recovered" during sleep after wakefulness? This question implies that being awake is associated with certain molecular, structural, or functional changes in the

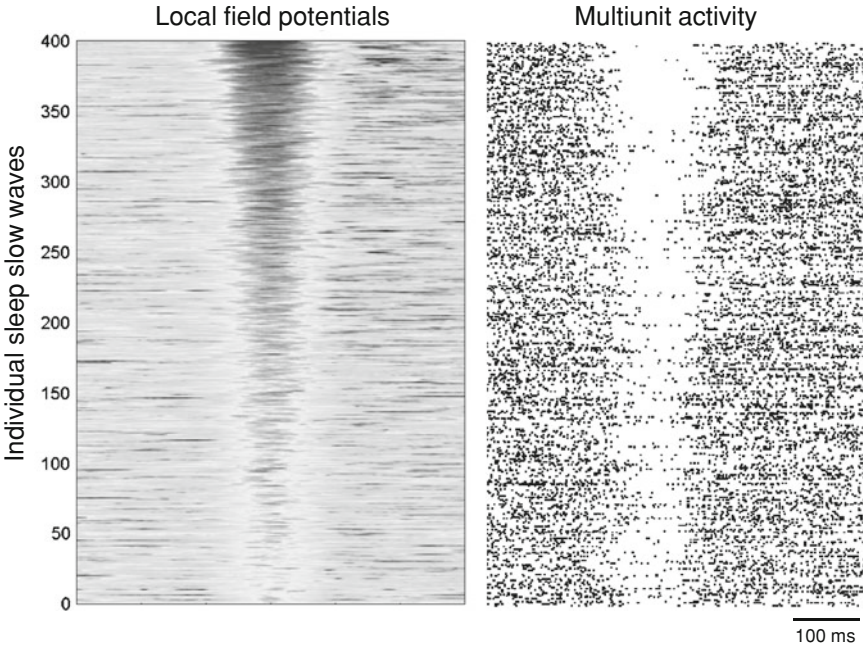

Fig. 2 *Left panel* individual local field potential slow waves during spontaneous NREM sleep in one individual rat. Four hundred slow waves were detected, and are sorted as a function of their amplitude (*gray intensity coded*, highest amplitude slow waves are on the *top*). *Right panel* corresponding raster plots of cortical multiunit activity. Note that high amplitude slow waves (*top*) are associated with longer silent periods across the recorded neuronal population

brain, which occur progressively and can only be reversed by sleep. The term "recovery" could either apply to specific measurable variables (from metabolic ones, such as cerebral glycogen stores, to cognitive ones, such as reaction times in the psychomotor vigilance task) or, in a broader sense, refer to an overall optimal waking function, which consists of many components and is determined by a variety of factors. The original notion that sleep has a homeostatic recovery function was proposed based on the observation that the levels of EEG slow wave activity during sleep increase in proportion to preceding waking duration and decrease during subsequent sleep. This relationship was mathematically formalized by using a simulation approach, where the temporal evolution of sleep–wake dependent process (so-called Process S) was modeled with a set of exponential functions using such parameters as time constants of an increase and a decrease, the lower and higher asymptote, and others (Borbély and Achermann 2005; Franken et al. 2001; Huber et al. 2000a; Rusterholz et al. 2010; Vyazovskiy et al. 2007a; Zavada et al. 2009). According to this model, sleep pressure, as reflected in SWA, increases during waking and decreases during sleep (Deboer 2013). Notably, NREM SWA increases after wakefulness not only in mammals, but also in birds (Jones et al. 2008; Martinez-Gonzalez et al. 2008).

It is now widely accepted that not only waking duration, but also waking quality is essential, such that the same duration of wake period can lead to markedly different sleep patterns if wake experience is qualitatively different. Important insights have been obtained from studies in which the content of waking experience was manipulated by inducing specific behaviors. For example, in one study rats were subjected to a stressful social defeat, which resulted in a substantial increase of subsequent EEG slow wave activity (Meerlo et al. 1997). More recently, it was found that the same amount of waking in the light and in the darkness appeared to lead to markedly different levels of SWA, which correlated with the amount of preceding exploratory behavior (Huber et al. 2007). Moreover, EEG theta activity, which is a marker of behavioral arousal and active locomotion, predicted the levels of SWA in subsequent sleep in rats subjected to chronic sleep restriction (Leemburg et al. 2010).

Notably, the association between the type of preceding activity and subsequent sleep is also apparent at a local level. Specifically, this was shown by performing finer topographic analyses, in experiments using selective local or peripheral stimulation, or in studies which recorded the activity of individual neurons (Krueger and Tononi 2011). Almost half a century ago, Giuseppe Moruzzi proposed that sleep might entail a cellular dimension: "sleep concerns primarily not the whole cerebrum, nor even the entire neocortex, but only those neurons or synapses, and possibly glia cells, which during wakefulness are responsible for the brain functions concerned with conscious behavior" (Moruzzi 1972). The local, use-dependent facet of sleep regulation had been suggested about 20 years ago, and since then it has received substantial experimental support (Krueger and Obal 1993; Krueger et al. 2008). The most appealing evidence for the local occurrence of sleep has been obtained from marine mammals, such as dolphins and seals, which exhibit unihemispheric slow wave activity while in water (Lyamin et al. 2012; Mukhametov et al. 1977). Such asymmetries appear to be homeostatically regulated, as manifested in a unilateral increase of SWA after selective suppression confined to one hemisphere (Oleksenko et al. 1992). Spontaneous interhemispheric asymmetries of the EEG during sleep have also been found , albeit to a much lesser extent, in birds (Rattenborg et al. 2001, 2012), humans, (Achermann et al. 2001; Nir et al. 2011) and rodents (Vyazovskiy et al. 2002a). In addition, strong anterior–posterior gradients in the expression of SWA have been shown in rodents (Huber et al. 2000b; Vyazovskiy et al. 2002a, b, 2004c, 2007c, 2008b; Vyazovskiy and Tobler 2005) and humans (Cajochen et al. 1999; Marzano et al. 2009; Massimini et al. 2004; Werth et al. 1996).

The evidence for a local, use- or activity- dependent increase in sleep slow wave activity has been obtained from several species and many experimental paradigms. For example, in both rats and mice, spontaneous unilateral whisker stimulation led to a significant increase in SWA over the stimulated somatosensory cortex during subsequent sleep (Vyazovskiy et al. 2000, 2004c). Rats trained to perform a skilled reaching task exhibit locally increased SWA in the primary motor cortex during post-training NREM sleep (Hanlon et al. 2009; Vyazovskiy and Tobler 2008). In humans, unilateral vibratory stimulation of the right hand led

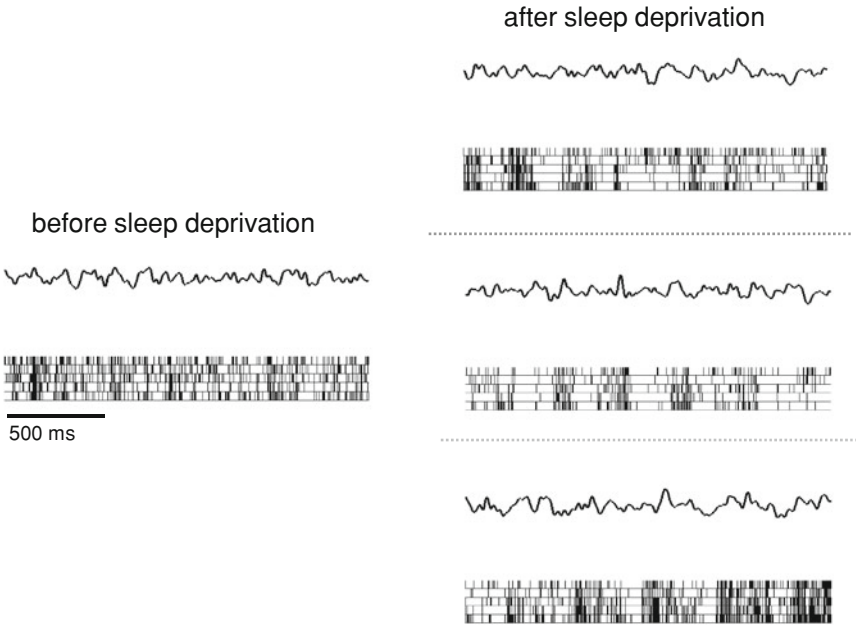

Fig. 3 *Left* a typical 2-s EEG trace and corresponding multiunit activity (MUA) recorded from the frontal motor cortex in one individual rat during waking at the beginning of sleep deprivation. *Right* three representative examples of EEG and MUA in an awake rat at the end of 4-h sleep deprivation. Note that despite wake-like EEG signals, the neuronal population often shows generalized quasi-synchronous cessation of neuronal firing, as during NREM sleep

to an increase in SWA over the left somatosensory area during subsequent sleep (Kattler et al. 1994). Moreover, a visuomotor learning task led to a local modulation in SWA during subsequent sleep that was significantly increased over the right parietal cortex (Huber et al. 2004). Conversely, following immobilization of one arm during the day, NREM sleep SWA was reduced over the corresponding contralateral somatosensory cortex (Huber et al. 2006). Finally, in rodents, local pharmacological manipulations of neuronal activity during waking altered the expression of sleep-like activity in the corresponding cortical areas (Churchill et al. 2008; Faraguna et al. 2008, 2010). Notably, signs of "local sleep" have been documented in behaviorally active animals (Pigarev et al. 1997; Vyazovskiy et al. 2011b; Vyazovskiy and Tobler 2008), suggesting that wakefulness is associated with an increasing drive to engage in a sleep-like mode of activity within specific neuronal circuits (Fig. 3). This notion was supported by a recent human study showing local, task-related changes in slow frequency EEG activity in awake subjects (Hung et al. 2013). The underlying mechanism of increased propensity to engage in down-states at a single neuron level is unknown but may be related to the growing need to obtain metabolic recovery or perform necessary cellular maintenance processes after sustained waking activity (Vyazovskiy and Harris 2013).

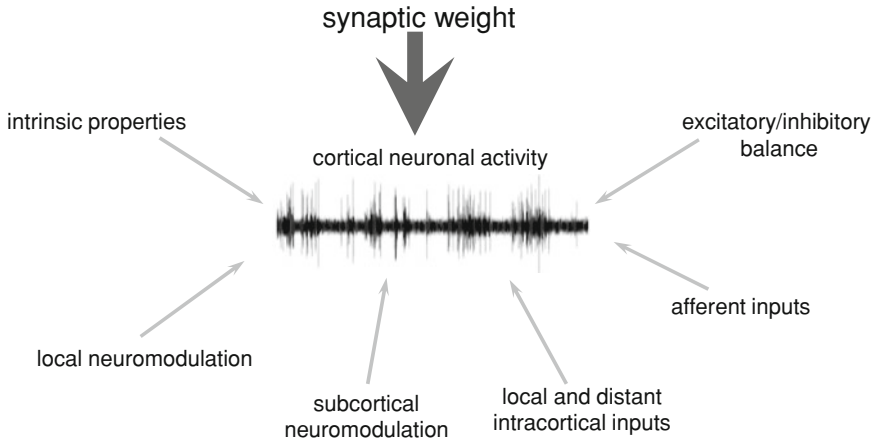

Fig. 4 Some of the essential factors that determine the occurrence of individual spikes, instantaneous changes in spiking activity, and long-term changes in neuronal responsiveness

Alternatively, or in addition, local changes in sleep-related activities may reflect synaptic changes.

4 Sleep, Neuroplasticity, and Synaptic Homeostasis

The ultimate function of neural or synaptic plasticity is to provide greater flexibility in the interaction of the organism with the constantly changing environment. It is not surprising, therefore, that several forms of neuroplasticity are highly conserved across evolution (Ebendal 1992; Qiu et al. 2006). It still remains to be established when neuronal plasticity first emerged, but it is undoubtedly present already in invertebrates (Bailey and Kandel 2008). Ultimately synaptic plasticity concerns the interaction between individual neurons. Within the brain, neurons integrate thousands of synaptic inputs from local and distant neurons at a timescale of milliseconds, but usually respond with only a few spikes per second. There are many intrinsic and extrinsic factors which influence neuronal spiking activity on a moment to moment basis (Fig. 4). However, even if all these factors remain stable, the capacity to respond to incoming inputs appears to be ultimately determined by the total synaptic weight impinging on a particular neuron, which must therefore be strictly regulated. Indeed, as the brain is constantly receiving sensory information, it must be continuously performing complex computational tasks, such as extracting relevant patterns of information from the multisensory world outside, determined by the context, future goals and preceding experience.

For synaptic plasticity to be beneficial, it must be regulated to prevent it from taking an aberrant form (Parent et al. 1997). Moreover, the regulation of net synaptic strength is vital for survival, inasmuch as it allows re-allocation of the

existing, limited amount of resources in a most efficient way, e.g., toward those neurons or local or distributed neuronal networks, which are most relevant for the ongoing behavior, or those, which were most affected by preceding activity. Dynamic adjustments of spiking outputs depending on the input can occur both on a fast scale, such as spike-frequency adaptation of individual neurons (Fuhrmann et al. 2002) and on a slower timescale, corresponding to homeostatic scaling (Turrigiano 1999) or Hebbian plasticity (Abbott and Nelson 2000). Homeostatic scaling refers to a mechanism, by which firing activity of individual neurons and neuronal circuits is maintained within a specific range, and has been demonstrated both in vitro and in vivo (Hengen et al. 2013; Ibata et al. 2008; Turrigiano 1999). In contrast, Hebbian mechanisms refer to a bidirectional form of plasticity, whereby the weight of synaptic connections between two neurons is increased or decreased depending on precise timing of their respective activities (Abbott and Nelson 2000; Caporale and Dan 2008). As the mechanisms of synaptic plasticity are highly elaborate (Malenka and Bear 2004; Turrigiano 2008), there is a great potential for malfunctioning (Nava and Roder 2011) and a breakdown in some key elements, such as signaling pathways (Lockett et al. 2010), or specific synaptic proteins (Bhakar et al. 2012) is detrimental. This may be manifested primarily in pathologic forms of activity incompatible with normal behaviors, and lead to neuronal damage, severe disease, or death.

Intriguingly, the general features aforementioned about plasticity largely apply to sleep as well. It is conserved across evolution (Cirelli and Tononi 2008; Tobler 2005), it is considered to be vitally important (Rechtschaffen et al. 1999), its mechanisms are highly complex (Brown et al. 2012), and it is prone to various disturbances (Porkka-Heiskanen et al. 2013). Finally, both neural plasticity and sleep are activity-dependent processes. As synaptic activity invariably leads to modifications of individual synapses potentially affecting neuronal spiking output, sleep invariably occurs after a certain amount of (waking) activity, and its major defining electrical event in mammals—EEG slow wave activity—is determined by preceding local neuronal activity. In fact, activity dependence of both plasticity and sleep are their most essential, if not defining features. On one hand, sustained synaptic activity invariably leads to some form of plastic changes. On the other hand, continuous physiological waking cannot be sustained for longer than a few hours or days and is consistently followed by local and global sleep (Cirelli and Tononi 2008).

5 Experimental Observations that can be Explained by Synaptic Homeostasis

The SHY reconciles many empirical observations concerning sleep and plasticity in a comprehensive theoretical framework. In the original formulation of the SHY proposed by Tononi and Cirelli in 2003, it had the following tenets: “(1) Wakefulness

is associated with synaptic potentiation in several cortical circuits; (2) Synaptic potentiation is tied to the homeostatic regulation of NREM sleep EEG slow wave activity; (3) Slow wave activity is associated with synaptic downscaling; (4) Synaptic downscaling is tied to the beneficial effects of sleep on neural function and, indirectly, on performance" (Tononi and Cirelli 2003). According to this hypothesis, a key variable that changes systematically during wakefulness, and must be restored back to baseline levels during sleep, is net synaptic weight. It is further suggested that since synaptic strength is tightly linked to energy needs, space, metabolic supplies, and, importantly, to the capacity for further plasticity, restoration of net synaptic strength by sleep would ultimately lead to renormalization of all these variables. The SHY has emerged as a conceptual shell based on a large body of disparate or unexplained findings accumulated over the last decades, and subsequently triggered intensive efforts in many laboratories around the world. Various models and experimental paradigms have been exploited in this framework—from single-cell recordings to complex cognitive tasks, and empirical observations have been obtained at several different levels: molecular, cellular, network, structural, functional, and behavioral. Each of these levels will be considered below, in an attempt to integrate them into a consistent picture.

5.1 Molecular Markers of Plasticity, Cellular Stress, and Sleep

Waking and sleep are associated with systematic changes in the expression and/or release of a variety of molecules, directly or indirectly involved in synaptic plasticity as well as in many other essential cellular functions. After the pioneering experiments by Giuditta et al., in the 1970s and 1980s, showing that overall RNA synthesis was increased during NREM sleep (Giuditta et al. 1980), a series of approaches including PCR, in situ hybridization, mRNA differential display and microarray have shown that several clusters of transcripts known to directly or indirectly influence plasticity are modulated across the sleep-wake cycle and after sleep deprivation. Among the established sleep-promoting substances is the tumor necrosis factor (TNF), which under physiological conditions increases during synaptic activity and can promote sleep when administered externally (Churchill et al. 2008; Krueger et al. 2001; Obal and Krueger 2003). While it remains to be determined to what extent TNF is essential for sleep regulation in physiological conditions, the involvement of TNF in the modulation of synaptic plasticity has been described (Stellwagen and Malenka 2006). Among the effects of TNF on plastic processes, a regulation of glutamate signaling by increasing expression of AMPA receptors has been reported (Pickering et al. 2005). Notably, in the rat cerebral cortex, the expression of GluR1-containing AMPA receptors were found to increase after waking (Vyazovskiy et al. 2008a). On the other hand, TNF-alpha administration led to a decrease in brain-derived neurotrophic factor (BDNF)

mRNA in several brain regions (Churchill et al. 2006). Several studies have shown that BDNF, which has been implicated in various forms of synaptic plasticity (Gomez-Palacio-Schjetnan and Escobar 2013), is expressed after sleep deprivation (Cirelli and Tononi 2000a), and especially after active exploratory waking (Huber et al. 2007), while its intracortical infusion enhances local sleep SWA (Faraguna et al. 2008). Also, the cortical expression of BDNF seems to parallel the homeostatic response to sleep deprivation in neonatal rats (Hairston et al. 2004). It should be noted, however, that another study showed that in the neocortex, neither 8 nor 48 h SD had significant effects on BDNF, Synapsin I or CAMKII mRNA levels (Guzman-Marin et al. 2006). In the hippocampus, the picture seems to also be complex: according to some reports BDNF appears to be down-regulated by 8 h of sleep deprivation (Alhaider et al. 2011; Guzman-Marin et al. 2006), while others detected an increase within both the cerebral cortex and the hippocampus (Cirelli et al. 2006; Cirelli and Tononi 2000a; Fujihara et al. 2003). Furthermore, one study found that 12 h SD significantly reduced hippocampal AMPA receptor phosphorylation at the GluR1-S845 site (Hagewoud et al. 2010). Together with TNF-alpha and BDNF, the list of molecules both involved in neuroplasticity and fluctuating across the sleep–wake cycle includes but is not limited to: Homer1a (Maret et al. 2007), Zif-268 (Ribeiro et al. 2002) and Arc (Ribeiro et al. 2007; Seibt et al. 2012). However, it remains to be determined whether the changes in these molecules are related to the proposed increase in synaptic strength or have other roles.

According to SHY, prolonged waking activity leads to increased synaptic strength and, as a result, increased spiking and synaptic activity (Vyazovskiy et al. 2009b). In order to sustain neuronal function at a higher level of excitability, cellular synthetic processes are likely to be intensified to provide additional receptors and synaptic vesicles components (Mackiewicz et al. 2007). Such changes could not only lead to plastic changes but may also be associated with cellular stress responses, and there is an intriguing possibility that some of their underlying mechanisms might overlap. Specifically, one of the well established effects of physiological waking or sleep deprivation is an up-regulation of molecules involved in the unfolded protein response (UPR) (Cirelli 2002; Cirelli and Tononi 2000b; Naidoo et al. 2005; Terao et al. 2003), which is an adaptive mechanism of cellular stress triggered when misfolded proteins accumulate in the lumen of the endoplasmic reticulum (Sidrauski et al. 1998; Vyazovskiy and Harris 2013; Walter and Ron 2011). The endoplasmic reticulum is an important organelle involved in neurotransmission and synaptic plasticity, which are regulated by Ca^{+2} release (Verkhratsky and Petersen 2002). Paracrine signaling mediated by activity-dependent release of molecules such as TNF may be directly involved in triggering UPR (Xue et al. 2005), and promote the occurrence of local sleep-like activity (Churchill et al. 2008). It is possible that local neuronal down-states may prevent synaptic strength from increasing further, thereby protecting neurons from pathological hyperexcitability. It was proposed recently that local sleep-like activity may enable cellular maintenance processes (Vyazovskiy and Harris 2013), which

could involve removal of AMPA receptors leading to a decrease in synaptic strength (Vyazovskiy et al. 2008a). The link between the changes at the level of protein synthesis and synaptic plasticity during waking has also been suggested by an increase in amyloid-beta during waking or sleep deprivation (Kang et al. 2009). It is possible that molecular chaperones, which constitute the primary biological defense against protein misfolding, and increase after waking (Terao et al. 2003) serve to protect the neurons from amyloid-beta aggregation as a result of intense synaptic activity during waking (Narayan et al. 2012). This notion is consistent with the hypothesis that increased neuronal activity during waking may lead to accumulation of protein fragments, which is reversed by sleep (Varshavsky 2012). Simpler preparations, such as in vitro neuronal cultures, which are capable of generating sustained sleep-like activity, appear to be a powerful model to address the link between specific patterns of network activity typical for waking and sleep and their corresponding molecular changes (Hinard et al. 2012).

5.2 Cellular Physiology and Sleep Homeostasis

In the last decades, much effort has been devoted to investigating state-dependent changes in the activity of individual cortical and subcortical neurons in vivo, in vitro, and under anesthesia. However, little has been done to address the effects of preceding history on the electrophysiological properties of individual neurons. More research is necessary since the effects observed may either arise from changes in (a) local or global neuromodulation, (b) neuronal excitability, (c) balance between excitation and inhibition, many other factors or their combined effects (Fig. 4). One possibility is that the effects of sleep–wake history on the electrophysiological properties of individual neurons could be mediated through voltage-dependent changes in the conformation of membrane-bound receptors (Rinne et al. 2013), which can be regulated by subcortical and cortical neuromodulation (McCormick 1992). Indeed, one study found that after 2 hours of sleep deprivation in young rats, the action of noradrenaline on the wake-promoting hypocretin/orexin (HCRT) neurons changed from excitation (75 % of cells) to inhibition (90 % of cells), and this effect was postsynaptic, as both excitatory and inhibitory responses persisted in tetrodotoxin or high magnesium/low calcium solutions (Grivel et al. 2005). This is an interesting observation, which could suggest that synaptic homeostasis in the neocortex may be regulated, at least in part, by functional changes controlled by subcortical neuromodulatory areas. A follow up study from the same group reported that sleep deprivation leads to an involvement of α_2-adrenoreceptors, which are responsible for hyperpolarization of the orexinergic neurons (Uschakov et al. 2011). The authors suggested that this mechanism could lead to a decrease of their firing activity, thereby indirectly promoting sleep. There is also evidence that direct measures of synaptic strength are affected by preceding sleep–wake history. For example, another recent study found that waking is associated with an increase in the strength of glutamatergic

synapses onto orexinergic neurons, as measured by an increase in amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs, "minis") (Rao et al. 2007). These results can suggest that sleep–wake history is an important determinant for the activity of various neuromodulatory subcortical systems, which are likely to be involved (directly or indirectly) in the plastic processes occurring during waking and sleep.

The SHY was addressed by several further studies, which attempted to directly assess various markers of synaptic strength at a single-cell level in the neocortex. Specifically, in one study, recordings from pyramidal cortical neurons in brain slices taken from sleeping and sleep-deprived mice and rats were performed. In all cases both frequency and amplitude of mEPSCs increased after waking and decreased after sleep, suggesting that a net increase in cortical synaptic strength occurs during waking both pre- and post-synaptically, while opposite changes occur during sleep (Liu et al. 2010). Interestingly, another study in mice found that after 8 h of partial sleep deprivation, achieved by a modified pedestal (flowerpot) over water method, the amplitude of miniature excitatory postsynaptic currents, recorded in layer V/VI pyramidal cells of the medial prefrontal cortex, were slightly reduced, while miniature inhibitory postsynaptic currents were unaffected, and intrinsic membrane excitability was increased (Winters et al. 2011). Thus, cortical areas and layers, neuronal subtypes, and their specific electrophysiological properties may be differentially affected by preceding waking activity. This is expected given the differences in the involvement of different neurons in specific activities, different patterns in their connectivity and other factors (Beltramo et al. 2013; Harris et al. 2011; Lapray et al. 2012; McCormick et al. 1985; Sakata and Harris 2009).

Unfortunately, existing patch clamp techniques (cell-attached or whole cell patch) do not allow continuous recording from single neurons across several hours—the timescale of the slow sleep-dependent homeostatic process. Performing long-term juxtacellular recordings is more feasible, but it has been mostly used to investigate state-dependent, rather than history-dependent changes in neuronal activity. For example, it was recently found in rats that parvalbumin-expressing basket GABA-ergic interneurons in the hippocampus change their firing consistent to changes in behavioral state (Lapray et al. 2012). Another rat study found that the activity (measured as c-Fos expression) of individual neurons located in the pre-optic and lateral hypothalamic areas, was dependent on preceding sleep deprivation or time spent in deep NREM sleep (Hsieh et al. 2011). Specifically, the percentage of activated cells in Median Preoptic Nucleus (MnPN) and ventrolateral preoptic area (VLPO) correlated significantly with time spent in deep NREM sleep during the 1 h prior to sacrifice. This observation is interesting, as it was shown earlier that bilateral lesions of the VLPO in rats resulted in a decrease of sleep time and sleep EEG SWA, which was proportional to the area that was lesioned (Lu et al. 2000). Moreover, it was shown recently, also in rats, that infusion of A_{2A} adenosine receptor antagonist into the VLPO attenuated the increase in neuronal discharge induced by sleep deprivation (Alam et al. 2014). Although specific mechanisms of these changes remain to be established, since the hypothalamus is implicated in the

regulation of state transitions (Saper et al. 2010), it is plausible that preceding history might affect both the strength of connectivity between cortical and subcortical neurons as well as the cortical neuromodulatory milieu, which could in turn promote sleep initiation, sleep maintenance, and sleep intensity.

5.3 Network Homeostasis

One of the most consistent observations in adult mammals is that sleep deprivation and prolonged physiological waking lead to increased EEG power in the slow wave range during subsequent sleep, which results from an increased incidence of high amplitude slow waves (Borbely et al. 1984; Huber et al. 2000b; Riedner et al. 2007; Vyazovskiy et al. 2006, 2007b; Vyazovskiy and Tobler 2005). Surprisingly, while increased SWA as a measure of preceding waking is well established, neither mechanistic explanation for it, nor its functional significance is clear.

As has been shown, EEG slow waves reflect the synchronous occurrence of down-states or off periods across large cortical populations (Buzsaki et al. 2012; Vyazovskiy et al. 2009b) (Figs. 1, 2). Anatomical studies suggest that the amplitude of slow wave activity can be accounted for by stronger connectivity between local and distant cortical regions (Piantoni et al. 2013; Vyazovskiy and Tobler 2005). Notably, it has been found that sleep with high SWA, such as under high sleep pressure, is characterized by increased local and global synchronization of cortical neuronal activity (Destexhe et al. 1999; Nir et al. 2011; Riedner et al. 2007; Vyazovskiy et al. 2004a, 2009b, 2011a), suggesting that either functional and/or anatomical connectivity is affected by preceding waking. It is important to emphasize that the slow oscillation is a network event, and for its expression it is essential that large, distributed interconnected neuronal populations engage in down-states near-simultaneously (Volgushev et al. 2006; Vyazovskiy and Harris 2013). The SHY provides a plausible mechanistic explanation for increased slow wave activity during early sleep after extended wakefulness (Esser et al. 2007; Hill and Tononi 2005; Riedner et al. 2007; Tononi and Cirelli 2006; Vyazovskiy et al. 2009a). Specifically, if cortical synaptic strength is affected by preceding waking or sleep, it would almost inevitably affect the local and global cortical dynamics, that would especially be apparent during spontaneous network activity during sleep (Vyazovskiy 2013; Vyazovskiy et al. 2011a).

Changes in the slope of slow waves usually parallel changes in slow wave amplitude. However, while slow wave slopes correlate with neuronal synchrony, the mechanisms underlying the changes in slow wave amplitude are less clear, and may be related to the duration of the population off periods (Vyazovskiy et al. 2009b). Indeed, although the higher amplitude of slow waves was often associated with steeper slope, this was not always the case, and several studies found steeper slopes after waking even after slow waves were matched by their amplitude (Esser et al. 2007; Riedner et al. 2007; Vyazovskiy et al. 2007b). While an LFP slope is an indirect measure of underlying neuronal synchrony, we also found that the

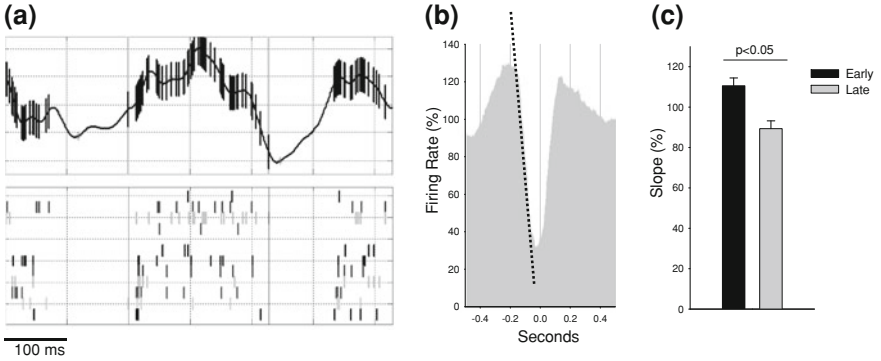

Fig. 5 **a** *Top panel* 600-ms record from the parietal EEG recorded in an individual rat during NREM sleep. Two individual slow waves (negativity downward) are apparent in this example. Vertical bars overlaid on the EEG trace denote the occurrences of neuronal spikes recorded concomitantly in the contralateral parietal cortex. *Bottom panel* raster plot of spiking activity of individual neurons shown on the *top panel*. Note that all neurons are silent during most of the downward deflection of the EEG signal, corresponding to slow waves. **b** An average profile of cortical multiunit activity (MUA) triggered by an occurrence of spontaneous EEG slow waves (time 0). Note that on average spiking activity during a slow wave is substantially decreased. *Dotted line* depicts the slope of the change in MUA corresponding to the downward slope of EEG slow wave. **c** Mean values (n = 4 rats) of the MUA slope (shown as *dotted line* on *panel B*) in early sleep (first 3 h period after light onset) and late sleep (last 3 h period of the same light period). Note that the MUA slope is more shallow in late sleep suggesting a decreased neuronal synchrony during the transition from network activity to network silence

slopes calculated based on the changes in cortical neuronal activity at on–off transitions also appear to be steeper in early sleep (Fig. 5).

It remains to be determined how the cortical networks self-organize in time and space to engage in synchronized slow wave activity, and what are the molecular mechanisms involved in synaptic plasticity, which are involved in this process. It was proposed recently that nitric oxide (NO), which is implicated strongly in synaptic plasticity in the cerebral cortex (Hardingham et al. 2013), may appear to be ideally placed to link homeostatic sleep drive with the observed changes in EEG SWA (Gerashchenko et al. 2008; Kilduff et al. 2011). Specifically, a novel sub-population of cortical inhibitory interneurons immunoreactive for neuronal nitric oxide synthase (nNOS) was found, which were activated after sleep deprivation in relation to cortical SWA (Morairty et al. 2013).

An essential step in the generation of slow wave activity is the initiation of an up state at the level of individual cortical neurons and its subsequent propagation across large cortical assemblies. It has been suggested that the onset of the up state is caused by a gradual membrane depolarization that builds up due to the summation of subthreshold events, which occur as a result of spontaneous neurotransmitter release (Chauvette et al. 2010; Timofeev et al. 2000). Once a subset of neurons enter an up state, they may be capable of recruiting other neurons, primarily those that receive the most dense or strongest projections from other

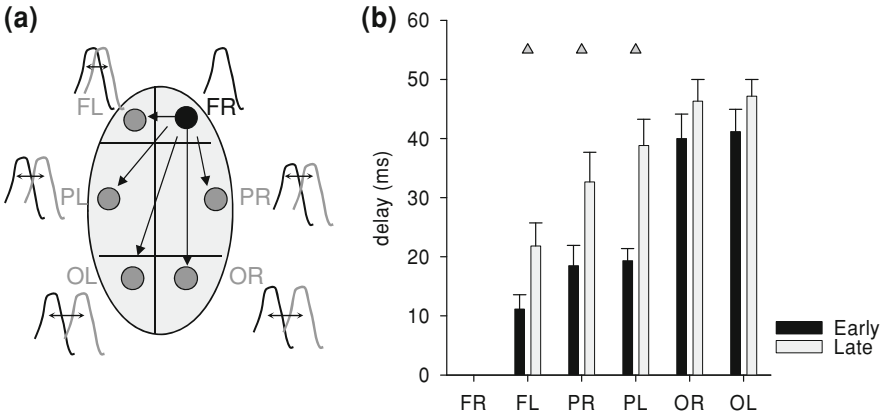

Fig. 6 **a** Schematic depiction of the position of six LFP bipolar concentric electrodes on the skull surface of a rat (*FR*, *FL* = frontal right, frontal left; *PR*, *PL* = parietal right, parietal left; *OR*, *OL* = occipital right, occipital left). *Right* frontal derivation was considered "origin" in this example, and sleep slow waves were detected in all six derivations. **b** The average delay was computed between the peaks of slow waves in FR and the peak of the next slow wave within the first 50 ms in the other five cortical derivations. Mean values ±SEM, n = 6 rats. Note that the delay was shortest for the slow wave in the contralateral frontal cortex, and longest for the most posterior occipital derivations. However, in late sleep (last 3 h period of the light period) the delay was significantly longer as compared to early sleep (first 3 h period of the light period)

neurons (Vyazovskiy et al. 2011b). Similarly, in humans and rats, a volley of locally applied electrical or magnetic activity, sufficiently strong to excite and recruit a large cortical neuronal population, is capable of inducing full-fledged EEG slow waves during natural sleep (Massimini et al. 2007; Vyazovskiy et al. 2009a). Notably, individual slow waves appear to have a unique site of origin and a distinct route of propagation, originating more frequently in the anterior cortical areas both in humans and in animals (Leemburg et al. 2010; Massimini et al. 2004; Murphy et al. 2009; Nir et al. 2011; Riedner et al. 2011; Vyazovskiy et al. 2009a). Consistently, the frontal areas of the neocortex have been described as more vulnerable to sleep loss (Anderson and Horne 2003; Horne 1993). Moreover, during sleep deprivation the frontal derivations show a more pronounced increase in slow EEG frequencies, which are considered a waking counterpart of "sleep pressure" (Finelli et al. 2000). Interestingly, spontaneous sleep slow waves appear to propagate from the site of origin to distant cortical areas faster in early sleep as compared to late sleep (Fig. 6), supporting the notion of stronger (or more efficacious) network connectivity after a period of waking. In addition to intracortical mechanisms, there is strong evidence for an involvement of the thalamus in generating cortical slow waves (Crunelli and Hughes 2009; David et al. 2013). It remains to be determined whether the strength of thalamocortical connections is also modified by preceding waking duration or sensory experience.

5.4 Neuronal Structural Modifications Across the Sleep–Wake Cycle

The cortical activity during sleep ultimately arises from the anatomical patterns of cortical connectivity (Kurth et al. 2010; Murphy et al. 2009; Piantoni et al. 2013; Rattenborg 2006; Vyazovskiy et al. 2004a; Vyazovskiy and Tobler 2005). While the changes in network activity after waking and sleep, as a result of plastic changes, can be partly accounted for by an alteration of functional connectivity or subtle modifications in molecular machinery, the question remains whether different behavioral states are also associated with dynamic anatomical changes. Indeed, while functional modifications of synapses can confer flexibility to cortical circuitries, morphological changes could provide greater stability. For example, given a powerful role of subcortical neuromodulation in voltage-dependent properties of postsynaptic receptors (McCormick 1992), subtle functional modifications may be vulnerable to unspecific generalized changes in cortical excitability. On the other hand, structural changes present a significant demand in terms of biosynthetic work and energy requirements necessary to maintain newly formed or existing spines, and therefore must be subject to regulation. Indeed, unlike other tissues, the space within the cranium is limited, precluding unrestricted increase in the number of synaptic spines as a result of waking experience. Do waking and sleep lead to structural changes at the level of individual neurons?

The first evidence for sleep–wake dependent structural changes in the central nervous system came from a confocal microscopic study in Drosophila, in which it was found that protein levels of several key components of central synapses, such as bruchpilot, cysteine string protein, disks-large, dynapsin, and syntaxin were high after waking and low after sleep (Gilestro et al. 2009). These changes were related to the preceding behavioral state rather than the time of day, and occurred in all major areas of the Drosophila brain. The decrease of synaptic markers during sleep was progressive, and sleep was necessary for their decline. Simultaneously, in a similar fruit fly model, another study showed that social experience did not only increase sleep, but was also associated with an increase in the number of synaptic terminals. Moreover, the number of synaptic terminals was reduced during sleep and this decline was prevented by sleep deprivation (Donlea et al. 2009). More recently Bushey et al. described, in three different Drosophila neuronal circuits, that synapse size or number increased after a few hours of waking and decreased only if flies were allowed to sleep, while rich wake experience resulted in both larger synaptic growth and greater sleep need (Bushey et al. 2011). Finally, using time-lapse two-photon imaging of the presynaptic marker synaptophysin in zebrafish larvae HCRT neurons, it was recently shown that synapse number is affected not only by the time of day but also by preceding sleep–wake history (Appelbaum et al. 2010).

Similar changes in structural synaptic plasticity were also obtained in rodents. Specifically, in adolescent mice, using two-photon microscopy, it was found that waking results in a net increase in cortical spines, whereas sleep is associated with

net spine loss (Maret et al. 2011; Yang and Gan 2012). Interestingly, the number of cortical spines did not change significantly across the sleep–wake cycle in adults, but only in adolescent mice, in which the turnover of spines is greater (Maret et al. 2011). This result indicates that, at least as far as superficial cortical layers are concerned, preceding history does not seem to lead to noticeable structural changes, and it may be that stronger stimulation or more intense waking experience is necessary for structural changes to be observed in adults animals. Moreover, the resolution of in vivo imaging techniques has so far prevented a systematic investigation of the effects of sleep and waking on synaptic volume, which could be modulated in the adult brain, similar to that seen for the number of synapses during adolescence. Interestingly, in the mouse olfactory bulb Yokoyama et al. found that elimination of adult-born granule cells occurs during postprandial behaviors, including sleep (Yokoyama et al. 2011), further suggesting that sleep may contribute to structural reorganization within the central nervous system. On the other hand, in the hippocampus prolonged sleep deprivation seems to reduce hippocampal cell proliferation, differentiation, and survival [for review see (Meerlo et al. 2009)].

5.5 Functional Implications

What are the functional consequences of plastic changes occurring during waking and sleep? Maintaining plastic changes within strictly controlled limits is not only important to assure sustainability of cortical circuits in terms of levels of excitability, availability of resources and brain "real estate" (Tononi and Cirelli 2003, 2006), but also in terms of functional consequences. While plastic changes may affect various aspects of brain physiology, the most important feature—the capacity for further change—deserves special attention.

Neuronal plasticity is manifested in several forms including potentiation and depression of synaptic transmission, which involve rapid adjustments in the strengths of individual synapses in response to specific patterns of correlated synaptic activity (Stellwagen and Malenka 2006), or in vivo experience (Rioult-Pedotti et al. 2000; Whitlock et al. 2006). An important property underlying long-term potentiation (LTP) is saturation, that is the relative inability to further enhance the amplitude of synaptic currents in response to a stimulus of increasing intensity or frequency (Heynen and Bear 2001). Saturation of both LTP and long-term depression (LTD) after repeated electrical or pharmacological stimulation was found in different species and preparations (Doyere et al. 1997; Frey et al. 1995; Heynen and Bear 2001; Lante et al. 2006; Moser et al. 1998).

A crucial observation was that the ability to learn and to induce LTP interact in a way suggestive of common substrates (Castro et al. 1989; Moser et al. 1998; Stefan et al. 2006; Ziemann 2004). For instance, after acquisition of a motor learning task both slope and amplitude of evoked potentials in the trained motor cortex increased relative to the contralateral, untrained one, suggesting the

occurrence of LTP (Rioult-Pedotti et al. 1998). To confirm this point, the authors showed that the ability to electrically induce LTP was reduced in the trained motor cortex, while LTD was enhanced. Similar results were obtained in the hippocampus (Whitlock et al. 2006). Notably, there is also evidence suggesting that LTP-like plasticity may be partially saturated after wakefulness even without any specific learning paradigm. Thus, in vitro studies in the hippocampus showed that insufficient or fragmented sleep impairs the induction of LTP but favors the induction of LTD [e.g., (Campbell et al. 2002; Kopp et al. 2006; McDermott et al. 2003; Tartar et al. 2006)]. An alternative explanation could be that other, yet unknown, processes at the molecular level interfere with or inhibit further synaptic strengthening after prolonged wakefulness.

It has been proposed that one of the functions for synaptic renormalization during sleep is to prevent LTP saturation, thereby allowing further plastic changes during subsequent wakefulness. This notion is consistent with the hypothesis that LTD may prime a synapse in preparation for the expression of LTP (Braunewell and Manahan-Vaughan 2001). Interestingly, several studies in humans showed an impairment of episodic memory after total sleep deprivation, suggesting that sleep before learning is critical in preparing the brain for the acquisition of new memories (Curcio et al. 2006; Huber 2007; Turner et al. 2007; Yoo et al. 2007). Consistently, recent studies in rats demonstrated that LTP was successfully induced after a period of sleep, but it was partially occluded after a period of wakefulness (Vyazovskiy et al. 2008a, 2011a). Thus, the partial inability for further plastic changes after waking and its restoration after sleep can be explained in the framework of the SHY. Although several results are functionally consistent with the SHY main claim, a set of data seems to be in open contradiction with it. For instance, Chauvette et al. showed that cortical somatosensory evoked potentials induced in cats by electrical stimulation of the medial lemniscus were enhanced after a brief period of sleep (Chauvette et al. 2012), leading the authors to conclude that sleep is associated with synaptic potentiation. An alternative interpretation could be that enhanced somatosensory responses after a "power nap" reflect temporarily, improved signal-to-noise ratio and increased fidelity in the transmission of sensory information from the periphery. More studies are necessary to address this inconsistency and to investigate the role of other possibly confounding factors, such as sleep inertia, brain temperature, or glucocorticoids.

5.6 Behavioral Homeostasis

The ultimate function of sleep is to enable optimal behavior during next day wakefulness. Crucially, complex behaviors are intimately related to plasticity, inasmuch as they serve adaptive purposes. As has been argued above, while many innate behaviors are available at the animal's disposal, it is more advantageous to leave "room" for acquisition of new schemes which are necessary for facing the

constantly changing environmental demands. During wakefulness, animals face environmental challenges that require an adequate behavioral response, and continuous behavioral adjustments involve learning, associated with neuronal plasticity (Whitlock et al. 2006). It is well established that sleep deprivation has serious consequences on subjective alertness, psychomotor vigilance, sustained attention, and many other cognitive functions (Killgore 2010; Lo et al. 2012; McCoy and Strecker 2011; Van Dongen et al. 2003). Thus, on one hand, behavior is inevitably associated with plastic changes in the relevant neural circuits, which occur during waking. On the other hand, they appear to be vulnerable to changes as waking time passes by. In this context two questions need to be addressed. First, is there a causal relationship between progressive incremental plastic changes during waking and impairments in cognition and behavior? Secondly, how can the behaviour benefit from synaptic homeostasis?

The challenge that necessarily has to be met is that it is difficult to disentangle the effects of preceding history from the ongoing behavioral state, which affects sensory function and motor output. Specifically, subjective experience, or behavioral performance can be temporarily restored even after a prolonged waking, for example by motivation or by administering wake-promoting substances. It has been shown that increased occurrence of local off periods within a specific cortical circuit correlates with reduced ability to perform a behavioral task (Vyazovskiy et al. 2011b). Such changes may occur in a use-dependent fashion: specifically, local wake "signature" of preceding activity has been shown recently in humans (Hung et al. 2013). Several studies suggest that network responsiveness to incoming inputs is modulated by the occurrence of off periods or slow waves (Massimini et al. 2003; Vyazovskiy et al. 2009a, 2013). It is possible, therefore, that the change in the balance of local and global interactions may not only lead to predictable sensory, behavioral and cognitive deficits, but also play a role in dynamic modifications of synaptic weights among distributed neuronal networks.

It is well known that attention is compromised after sleep deprivation, although underlying mechanisms remain unknown (McCoy and Strecker 2011). One possibility is that prolonged waking results in a global and unspecific synchronization between large neuronal populations, while gating relevant inputs requires local desynchronization and a highly selective synchronization among specific neuronal populations within a specific frequency range (Harris and Thiele 2011). Moreover, individual neurons vary in their responses to a specific stimulus, and the relative precision is achieved by "averaging" at the level of the whole population. However, if the functional connectivity between neurons is increased, a strong bias is introduced precipitating erroneous summed output, that could lead to longer reaction times or mistakes. Finally, local sleep at an individual neuron level may lead to a failure to respond or a stronger, but less selective response depending on the phase of ongoing population activity (Vyazovskiy et al. 2013).

Thus, if waking is associated with progressively increased synaptic strength, this could lead to a progressive increase in the number of neuronal off periods, that would alter dynamic relationships between critical networks, thereby precipitating behavioral deficits. Impaired performance due to the occurrence of local sleep

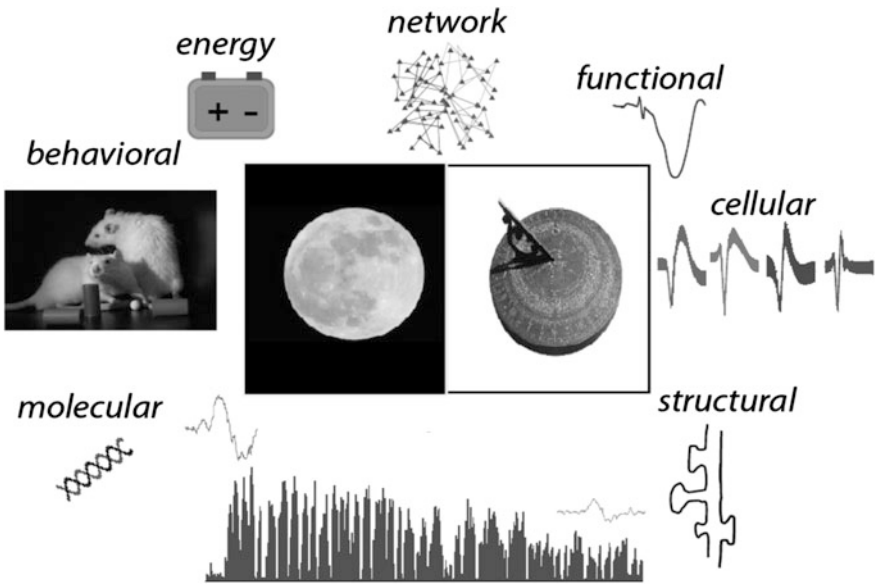

Fig. 7 According to the Synaptic Homeostasis Hypothesis, wakefulness is associated with a net increase in synaptic strength, while sleep leads to synaptic renormalization. The hypothesis is supported by several lines of evidence, such as altered expression of plasticity-related genes (*molecular*), changes in the pattern of activity of individual neurons (*cellular*), dendritic spines turnover (*structural*), local and global neuronal synchronization (*network*), saturation of synaptic responses (*functional*), increased energy requirements, and behavioral/learning impairments. The process of synaptic renormalization during sleep is hypothesized to be reflected in progressive homeostatic decrease of cortical EEG slow wave activity (*bottom*)

could, in turn, play the physiological role of a "sensing mechanism" by signaling the necessity to engage in a global sleep (Vyazovskiy and Tobler 2012). The process of synaptic renormalization occurring during sleep, by reducing net synaptic strength, would lead to an elimination of local off periods, restoring normal behavioral performance.

6 Conclusions

The ultimate function of wakefulness is to enable efficient interaction of the organism with the environment, which requires elaborate and diverse forms of neuronal plasticity. As sleep is necessary to enable normal waking functioning, and on the other hand depends on preceding waking, it is highly unlikely that it is not involved, directly or indirectly, in the regulation of neural plasticity. It should be emphasized that sleep is a highly complex phenomenon, occurring at many different spatial and temporal scales. Most existing hypotheses for the function of

sleep take into account only a small part of the broad repertoire of changes typical for sleep, such as cortico–hippocampal interactions, or reduced metabolism. However, in order to address sleep's function in a comprehensive way, a framework is necessary that reconciles such different phenomena as gene expression, fine synaptic modifications, activity of single cells and large networks, and whole animal behavior in a unified coherent picture. The SHY provides one such framework (Fig. 7).

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References

Abbott LF, Nelson SB (2000) Synaptic plasticity: taming the beast. Nat Neurosci 3(Suppl):1178–1183

Abel T, Havekes R, Saletin JM, Walker MP (2013) Sleep, plasticity and memory from molecules to whole-brain networks. Curr Biol 23:R774–R788

Achermann P, Finelli LA, Borbely AA (2001) Unihemispheric enhancement of delta power in human frontal sleep EEG by prolonged wakefulness. Brain Res 913:220–223

Alam MA, Kumar S, McGinty D, Alam MN, Szymusiak R (2014) Neuronal activity in the preoptic hypothalamus during sleep deprivation and recovery sleep. J Neurophysiol 111:287–299

Alhaider IA, Aleisa AM, Tran TT, Alkadhi KA (2011) Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. Mol Cell Neurosci 46:742–751

Anderson C, Horne JA (2003) Prefrontal cortex: links between low frequency delta EEG in sleep and neuropsychological performance in healthy, older people. Psychophysiology 40:349–357

Appelbaum L, Wang G, Yokogawa T, Skariah GM, Smith SJ, Mourrain P, Mignot E (2010) Circadian and homeostatic regulation of structural synaptic plasticity in hypocretin neurons. Neuron 68:87–98

Bailey CH, Kandel ER (2008) Synaptic remodeling, synaptic growth and the storage of long-term memory in Aplysia. Prog Brain Res 169:179–198

Beltramo R, D'Urso G, Dal Maschio M, Farisello P, Bovetti S, Clovis Y, Lassi G, Tucci V, De Pietri Tonelli D, Fellin T (2013) Layer-specific excitatory circuits differentially control recurrent network dynamics in the neocortex. Nat Neurosci 16:227–234

Bhakar AL, Dolen G, Bear MF (2012) The pathophysiology of fragile X (and what it teaches us about synapses). Annu Rev Neurosci 35:417–443

Borbely AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195–204

Borbély AA, Achermann P (2005) Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W. B. Saunders, Philadelphia, pp 405–417

Borbely AA, Tobler I, Hanagasioglu M (1984) Effect of sleep deprivation on sleep and EEG power spectra in the rat. Behav Brain Res 14:171–182

Borbely AA, Tononi G (1998) The quest for the essence of sleep. Daedalus 127:167–196

Braunewell KH, Manahan-Vaughan D (2001) Long-term depression: a cellular basis for learning? Rev Neurosci 12:121–140

Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW (2012) Control of sleep and wakefulness. Physiol Rev 92:1087–1187

Bushey D, Tononi G, Cirelli C (2011) Sleep and synaptic homeostasis: structural evidence in Drosophila. Science 332:1576–1581
Buzsaki G, Anastassiou CA, Koch C (2012) The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. Nat Rev Neurosci 13:407–420
Cajochen C, Foy R, Dijk DJ (1999) Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. Sleep Res Online 2:65–69
Campbell IG, Guinan MJ, Horowitz JM (2002) Sleep deprivation impairs long-term potentiation in rat hippocampal slices. J Neurophysiol 88:1073–1076
Caporale N, Dan Y (2008) Spike timing-dependent plasticity: a Hebbian learning rule. Annu Rev Neurosci 31:25–46
Castro CA, Silbert LH, McNaughton BL, Barnes CA (1989) Recovery of spatial learning deficits after decay of electrically induced synaptic enhancement in the hippocampus. Nature 342:545–548
Chauvette S, Seigneur J, Timofeev I (2012) Sleep oscillations in the thalamocortical system induce long-term neuronal plasticity. Neuron 75:1105–1113
Chauvette S, Volgushev M, Timofeev I (2010) Origin of active states in local neocortical networks during slow sleep oscillation. Cereb Cortex 20:2660–2674
Churchill L, Rector DM, Yasuda K, Fix C, Rojas MJ, Yasuda T, Krueger JM (2008) Tumor necrosis factor alpha: activity dependent expression and promotion of cortical column sleep in rats. Neuroscience 156:71–80
Churchill L, Taishi P, Wang M, Brandt J, Cearley C, Rehman A, Krueger JM (2006) Brain distribution of cytokine mRNA induced by systemic administration of interleukin-1beta or tumor necrosis factor alpha. Brain Res 1120:64–73
Cirelli C (2002) How sleep deprivation affects gene expression in the brain: a review of recent findings. J Appl Physiol 92:394–400
Cirelli C, Faraguna U, Tononi G (2006) Changes in brain gene expression after long-term sleep deprivation. J Neurochem 98:1632–1645
Cirelli C, Tononi G (2000a) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. J Neurosci 20:9187–9194
Cirelli C, Tononi G (2000b) Gene expression in the brain across the sleep–waking cycle. Brain Res 885:303–321
Cirelli C, Tononi G (2008) Is sleep essential? PLoS Biol 6:e216
Crunelli V, Hughes SW (2009) The slow (<1 Hz) rhythm of non-REM sleep: a dialogue between three cardinal oscillators. Nat Neurosci 13:9–17
Curcio G, Ferrara M, De Gennaro L (2006) Sleep loss, learning capacity and academic performance. Sleep Med Rev 10:323–337
Daan S, Beersma DG, Borbely AA (1984) Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 246:R161–R183
David F, Schmiedt JT, Taylor HL, Orban G, Di Giovanni G, Uebele VN, Renger JJ, Lambert RC, Leresche N, Crunelli V (2013) Essential thalamic contribution to slow waves of natural sleep. J Neurosci 33:19599–19610
Deboer T (2013) Behavioral and electrophysiological correlates of sleep and sleep homeostasis. Curr Top Behav Neurosci. doi:10.1007/7854_2013_248
Destexhe A, Contreras D, Steriade M (1999) Spatiotemporal analysis of local field potentials and unit discharges in cat cerebral cortex during natural wake and sleep states. J Neurosci 19:4595–4608
Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126
Donlea JM, Ramanan N, Shaw PJ (2009) Use-dependent plasticity in clock neurons regulates sleep need in Drosophila. Science 324:105–108
Doyere V, Srebro B, Laroche S (1997) Heterosynaptic LTD and depotentiation in the medial perforant path of the dentate gyrus in the freely moving rat. J Neurophysiol 77:571–578
Ebendal T (1992) Function and evolution in the NGF family and its receptors. J Neurosci Res 32:461–470

Esser SK, Hill SL, Tononi G (2007) Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. Sleep 30:1617–1630

Faraguna U, Nelson A, Vyazovskiy VV, Cirelli C, Tononi G (2010) Unilateral cortical spreading depression affects sleep need and induces molecular and electrophysiological signs of synaptic potentiation in vivo. Cereb Cortex 20:2939–2947

Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C (2008) A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. J Neurosci 28:4088–4095

Finelli LA, Baumann H, Borbely AA, Achermann P (2000) Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. Neuroscience 101:523–529

Frank MG (2006) The mystery of sleep function: current perspectives and future directions. Rev Neurosci 17:375–392

Franken P, Chollet D, Tafti M (2001) The homeostatic regulation of sleep need is under genetic control. J Neurosci 21:2610–2621

Frey U, Schollmeier K, Reymann KG, Seidenbecher T (1995) Asymptotic hippocampal long-term potentiation in rats does not preclude additional potentiation at later phases. Neuroscience 67:799–807

Fuhrmann G, Markram H, Tsodyks M (2002) Spike frequency adaptation and neocortical rhythms. J Neurophysiol 88:761–770

Fujihara H, Sei H, Morita Y, Ueta Y, Morita K (2003) Short-term sleep disturbance enhances brain-derived neurotrophic factor gene expression in rat hippocampus by acting as internal stressor. J Mol Neurosci 21:223–232

Gerashchenko D, Wisor JP, Burns D, Reh RK, Shiromani PJ, Sakurai T, de la Iglesia HO, Kilduff TS (2008) Identification of a population of sleep-active cerebral cortex neurons. Proc Natl Acad Sci USA 105:10227–10232

Gilestro GF, Tononi G, Cirelli C (2009) Widespread changes in synaptic markers as a function of sleep and wakefulness in Drosophila. Science 324:109–112

Giuditta A, Rutigliano B, Vitale-Neugebauer A (1980) Influence of synchronized sleep on the biosynthesis of RNA in neuronal and mixed fractions isolated from rabbit cerebral cortex. J Neurochem 35:1267–1272

Gomez-Palacio-Schjetnan A, Escobar ML (2013) Neurotrophins and synaptic plasticity. Curr Top Behav Neurosci 15:117–136

Green JD, Arduini AA (1954) Hippocampal electrical activity in arousal. J Neurophysiol 17:533–557

Grivel J, Cvetkovic V, Bayer L, Machard D, Tobler I, Muhlethaler M, Serafin M (2005) The wake-promoting hypocretin/orexin neurons change their response to noradrenaline after sleep deprivation. J Neurosci 25:4127–4130

Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol 575:807–819

Hagewoud R, Havekes R, Novati A, Keijser JN, Van der Zee EA, Meerlo P (2010) Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. J Sleep Res 19:280–288

Haider B, Duque A, Hasenstaub AR, McCormick DA (2006) Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. J Neurosci 26:4535–4545

Hairston IS, Peyron C, Denning DP, Ruby NF, Flores J, Sapolsky RM, Heller HC, O'Hara BF (2004) Sleep deprivation effects on growth factor expression in neonatal rats: a potential role for BDNF in the mediation of delta power. J Neurophysiol 91:1586–1595

Hanlon EC, Faraguna U, Vyazovskiy VV, Tononi G, Cirelli C (2009) Effects of skilled training on sleep slow wave activity and cortical gene expression in the rat. Sleep 32:719–729

Hardingham N, Dachtler J, Fox K (2013) The role of nitric oxide in pre-synaptic plasticity and homeostasis. Front Cell Neurosci 7:190

Harris KD, Bartho P, Chadderton P, Curto C, de la Rocha J, Hollender L, Itskov V, Luczak A, Marguet SL, Renart A et al (2011) How do neurons work together? Lessons from auditory cortex. Hear Res 271:37–53

Harris KD, Thiele A (2011) Cortical state and attention. Nat Rev Neurosci 12:509–523

Hengen KB, Lambo ME, Van Hooser SD, Katz DB, Turrigiano GG (2013) Firing rate homeostasis in visual cortex of freely behaving rodents. Neuron 80:335–342

Heynen AJ, Bear MF (2001) Long-term potentiation of thalamocortical transmission in the adult visual cortex in vivo. J Neurosci 21:9801–9813

Hill S, Tononi G (2005) Modeling sleep and wakefulness in the thalamocortical system. J Neurophysiol 93:1671–1698

Hinard V, Mikhail C, Pradervand S, Curie T, Houtkooper RH, Auwerx J, Franken P, Tafti M (2012) Key electrophysiological, molecular, and metabolic signatures of sleep and wakefulness revealed in primary cortical cultures. J Neurosci 32:12506–12517

Hobson JA, McCarley RW (1971) Cortical unit activity in sleep and waking. Electroencephalogr Clin Neurophysiol 30:97–112

Horne JA (1993) Human sleep, sleep loss and behaviour. Implications for the prefrontal cortex and psychiatric disorder. Br J Psychiatry 162:413–419

Hsieh KC, Gvilia I, Kumar S, Uschakov A, McGinty D, Alam MN, Szymusiak R (2011) c-Fos expression in neurons projecting from the preoptic and lateral hypothalamic areas to the ventrolateral periaqueductal gray in relation to sleep states. Neuroscience 188:55–67

Huber R (2007) Memory formation: sleep enough before learning. Curr Biol 17:R367–R368

Huber R, Deboer T, Tobler I (2000a) Effects of sleep deprivation on sleep and sleep EEG in three mouse strains: empirical data and simulations. Brain Res 857:8–19

Huber R, Deboer T, Tobler I (2000b) Topography of EEG dynamics after sleep deprivation in mice. J Neurophysiol 84:1888–1893

Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, Tononi G (2006) Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nat Neurosci 9:1169–1176

Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78–81

Huber R, Tononi G, Cirelli C (2007) Exploratory behavior, cortical BDNF expression, and sleep homeostasis. Sleep 30:129–139

Hung CS, Sarasso S, Ferrarelli F, Riedner B, Ghilardi MF, Cirelli C, Tononi G (2013) Local experience-dependent changes in the wake EEG after prolonged wakefulness. Sleep 36:59–72

Ibata K, Sun Q, Turrigiano GG (2008) Rapid synaptic scaling induced by changes in postsynaptic firing. Neuron 57:819–826

Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10:100–107

Jones BE (2005) From waking to sleeping: neuronal and chemical substrates. Trends Pharmacol Sci 26:578–586

Jones SG, Vyazovskiy VV, Cirelli C, Tononi G, Benca RM (2008) Homeostatic regulation of sleep in the white-crowned sparrow (Zonotrichia leucophrys gambelii). BMC Neurosci 9:47

Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM (2009) Amyloid-beta dynamics are regulated by orexin and the sleep–wake cycle. Science 326:1005–1007

Kattler H, Dijk DJ, Borbely AA (1994) Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. J Sleep Res 3:159–164

Kilduff TS, Cauli B, Gerashchenko D (2011) Activation of cortical interneurons during sleep: an anatomical link to homeostatic sleep regulation? Trends Neurosci 34:10–19

Killgore WD (2010) Effects of sleep deprivation on cognition. Prog Brain Res 185:105–129

Kopp C, Longordo F, Nicholson JR, Luthi A (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. J Neurosci 26:12456–12465

Krueger JM, Obal F (1993) A neuronal group theory of sleep function. J Sleep Res 2:63–69

Krueger JM, Obal FJ, Fang J, Kubota T, Taishi P (2001) The role of cytokines in physiological sleep regulation. Ann N Y Acad Sci 933:211–221

Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, Panksepp J (2008) Sleep as a fundamental property of neuronal assemblies. Nat Rev Neurosci 9:910–919

Krueger JM, Tononi G (2011) Local use-dependent sleep; synthesis of the new paradigm. Curr Top Med Chem 11:2490–2492

Kurth S, Ringli M, Geiger A, LeBourgeois M, Jenni OG, Huber R (2010) Mapping of cortical activity in the first two decades of life: a high-density sleep electroencephalogram study. J Neurosci 30:13211–13219

Lante F, Cavalier M, Cohen-Solal C, Guiramand J, Vignes M (2006) Developmental switch from LTD to LTP in low frequency-induced plasticity. Hippocampus 16:981–989

Lapray D, Lasztoczi B, Lagler M, Viney TJ, Katona L, Valenti O, Hartwich K, Borhegyi Z, Somogyi P, Klausberger T (2012) Behavior-dependent specialization of identified hippocampal interneurons. Nat Neurosci 15:1265–1271

Leemburg S, Vyazovskiy VV, Olcese U, Bassetti CL, Tononi G, Cirelli C (2010) Sleep homeostasis in the rat is preserved during chronic sleep restriction. Proc Natl Acad Sci U S A 107:15939–15944

Liu ZW, Faraguna U, Cirelli C, Tononi G, Gao XB (2010) Direct evidence for wake-related increases and sleep-related decreases in synaptic strength in rodent cortex. J Neurosci 30:8671–8675

Lo JC, Groeger JA, Santhi N, Arbon EL, Lazar AS, Hasan S, von Schantz M, Archer SN, Dijk DJ (2012) Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. PLoS One 7:e45987

Lockett GA, Wilkes F, Maleszka R (2010) Brain plasticity, memory and neurological disorders: an epigenetic perspective. NeuroReport 21:909–913

Lu J, Greco MA, Shiromani P, Saper CB (2000) Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. J Neurosci 20:3830–3842

Lyamin OI, Pavlova IF, Kosenko PO, Mukhametov LM, Siegel JM (2012) Regional differences in cortical electroencephalogram (EEG) slow wave activity and interhemispheric EEG asymmetry in the fur seal. J Sleep Res 21:603–611

Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI (2007) Macromolecule biosynthesis: a key function of sleep. Physiol Genomics 31:441–457

Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44:5–21

Maret S, Dorsaz S, Gurcel L, Pradervand S, Petit B, Pfister C, Hagenbuchle O, O'Hara BF, Franken P, Tafti M (2007) Homer1a is a core brain molecular correlate of sleep loss. Proc Natl Acad Sci USA 104:20090–20095

Maret S, Faraguna U, Nelson AB, Cirelli C, Tononi G (2011) Sleep and waking modulate spine turnover in the adolescent mouse cortex. Nat Neurosci 14:1418–1420

Martinez-Gonzalez D, Lesku JA, Rattenborg NC (2008) Increased EEG spectral power density during sleep following short-term sleep deprivation in pigeons (Columba livia): evidence for avian sleep homeostasis. J Sleep Res 17:140–153

Marzano C, Ferrara M, Curcio G, Gennaro LD (2009) The effects of sleep deprivation in humans: topographical electroencephalogram changes in non-rapid eye movement (NREM) sleep versus REM sleep. J Sleep Res 19:260–268

Massimini M, Ferrarelli F, Esser SK, Riedner BA, Huber R, Murphy M, Peterson MJ, Tononi G (2007) Triggering sleep slow waves by transcranial magnetic stimulation. Proc Natl Acad Sci USA 104:8496–8501

Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G (2004) The sleep slow oscillation as a traveling wave. J Neurosci 24:6862–6870

Massimini M, Rosanova M, Mariotti M (2003) EEG slow (approximately 1 Hz) waves are associated with nonstationarity of thalamo-cortical sensory processing in the sleeping human. J Neurophysiol 89:1205–1213

McCormick DA (1992) Neurotransmitter actions in the thalamus and cerebral cortex. J Clin Neurophysiol 9:212–223
McCormick DA, Connors BW, Lighthall JW, Prince DA (1985) Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. J Neurophysiol 54:782–806
McCoy JG, Strecker RE (2011) The cognitive cost of sleep lost. Neurobiol Learn Mem 96:564–582
McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003) Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 23:9687–9695
Meerlo P, Mistlberger RE, Jacobs BL, Heller HC, McGinty D (2009) New neurons in the adult brain: the role of sleep and consequences of sleep loss. Sleep Med Rev 13:187–194
Meerlo P, Pragt BJ, Daan S (1997) Social stress induces high intensity sleep in rats. Neurosci Lett 225:41–44
Mignot E (2008) Why we sleep: the temporal organization of recovery. PLoS Biol 6:e106
Morairty SR, Dittrich L, Pasumarthi RK, Valladao D, Heiss JE, Gerashchenko D, Kilduff TS (2013) A role for cortical nNOS/NK1 neurons in coupling homeostatic sleep drive to EEG slow wave activity. Proc Natl Acad Sci USA 110:20272–20277
Moruzzi G (1972) Sleep–Waking Cycle. Ergebnisse Der Physiologie Biologischen Chemie Und Experimentellen Pharmakologie 64:1–165
Moser EI, Krobert KA, Moser MB, Morris RG (1998) Impaired spatial learning after saturation of long-term potentiation. Science 281:2038–2042
Mukhametov LM, Supin AY, Polyakova IG (1977) Interhemispheric asymmetry of the electroencephalographic sleep patterns in dolphins. Brain Res 134:581–584
Murphy M, Riedner BA, Huber R, Massimini M, Ferrarelli F, Tononi G (2009) Source modeling sleep slow waves. Proc Natl Acad Sci USA 106:1608–1613
Naidoo N, Giang W, Galante RJ, Pack AI (2005) Sleep deprivation induces the unfolded protein response in mouse cerebral cortex. J Neurochem 92:1150–1157
Narayan P, Meehan S, Carver JA, Wilson MR, Dobson CM, Klenerman D (2012) Amyloid-beta oligomers are sequestered by both intracellular and extracellular chaperones. Biochemistry 51:9270–9276
Nava E, Roder B (2011) Adaptation and maladaptation insights from brain plasticity. Prog Brain Res 191:177–194
Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, Tononi G (2011) Regional slow waves and spindles in human sleep. Neuron 70:153–169
Nir Y, Vyazovskiy VV, Cirelli C, Banks MI, Tononi G (2013) Auditory Responses and stimulus-specific adaptation in rat auditory cortex are preserved across NREM and REM sleep. Cereb Cortex (in press)
Noda H, Adey WR (1970) Firing of neuron pairs in cat association cortex during sleep and wakefulness. J Neurophysiol 33:672–684
Obal F Jr, Krueger JM (2003) Biochemical regulation of non-rapid-eye-movement sleep. Front Biosci 8:d520–d550
Okun M, Lampl I (2008) Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities. Nat Neurosci 11:535–537
Oleksenko AI, Mukhametov LM, Polyakova IG, Supin AY, Kovalzon VM (1992) Unihemispheric sleep deprivation in bottlenose dolphins. J Sleep Res 1:40–44
Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH (1997) Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. J Neurosci 17:3727–3738
Petersen CC, Hahn TT, Mehta M, Grinvald A, Sakmann B (2003) Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex. Proc Natl Acad Sci U S A 100:13638–13643
Piantoni G, Poil SS, Linkenkaer-Hansen K, Verweij IM, Ramautar JR, Van Someren EJ, Van Der Werf YD (2013) Individual differences in white matter diffusion affect sleep oscillations. J Neurosci 33:227–233

Pickering M, Cumiskey D, O'Connor JJ (2005) Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. Exp Physiol 90:663–670

Pigarev IN, Nothdurft HC, Kastner S (1997) Evidence for asynchronous development of sleep in cortical areas. NeuroReport 8:2557–2560

Porkka-Heiskanen T, Zitting KM, Wigren HK (2013) Sleep, its regulation and possible mechanisms of sleep disturbances. Acta Physiol (Oxf) 208:311–328

Qiu S, Korwek KM, Weeber EJ (2006) A fresh look at an ancient receptor family: emerging roles for low density lipoprotein receptors in synaptic plasticity and memory formation. Neurobiol Learn Mem 85:16–29

Rao Y, Liu ZW, Borok E, Rabenstein RL, Shanabrough M, Lu M, Picciotto MR, Horvath TL, Gao XB (2007) Prolonged wakefulness induces experience-dependent synaptic plasticity in mouse hypocretin/orexin neurons. J Clin Invest 117:4022–4033

Rattenborg NC (2006) Evolution of slow-wave sleep and palliopallial connectivity in mammals and birds: a hypothesis. Brain Res Bull 69:20–29

Rattenborg NC, Amlaner CJ, Lima SL (2001) Unilateral eye closure and interhemispheric EEG asymmetry during sleep in the pigeon (Columba livia). Brain Behav Evol 58:323–332

Rattenborg NC, Lima SL, Lesku JA (2012) Sleep locally, act globally. Neuroscientist 18:533–546

Rechtschaffen A, Bergmann BM, Gilliland MA, Bauer K (1999) Effects of method, duration, and sleep stage on rebounds from sleep deprivation in the rat. Sleep 22:11–31

Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. J Neurosci 22:10914–10923

Ribeiro S, Shi X, Engelhard M, Zhou Y, Zhang H, Gervasoni D, Lin SC, Wada K, Lemos NA, Nicolelis MA (2007) Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. Front Neurosci 1:43–55

Riedner BA, Hulse BK, Murphy MJ, Ferrarelli F, Tononi G (2011) Temporal dynamics of cortical sources underlying spontaneous and peripherally evoked slow waves. Prog Brain Res 193:201–218

Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, Tononi G (2007) Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep 30:1643–1657

Rinne A, Birk A, Bunemann M (2013) Voltage regulates adrenergic receptor function. Proc Natl Acad Sci USA 110:1536–1541

Rioult-Pedotti MS, Friedman D, Donoghue JP (2000) Learning-induced LTP in neocortex. Science 290:533–536

Rioult-Pedotti MS, Friedman D, Hess G, Donoghue JP (1998) Strengthening of horizontal cortical connections following skill learning. Nat Neurosci 1:230–234

Rusterholz T, Durr R, Achermann P (2010) Inter-individual differences in the dynamics of sleep homeostasis. Sleep 33:491–498

Sakata S, Harris KD (2009) Laminar structure of spontaneous and sensory-evoked population activity in auditory cortex. Neuron 64:404–418

Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE (2010) Sleep state switching. Neuron 68:1023–1042

Seibt J, Dumoulin MC, Aton SJ, Coleman T, Watson A, Naidoo N, Frank MG (2012) Protein synthesis during sleep consolidates cortical plasticity in vivo. Curr Biol 22:676–682

Sidrauski C, Chapman R, Walter P (1998) The unfolded protein response: an intracellular signalling pathway with many surprising features. Trends Cell Biol 8:245–249

Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsaki G (2008) Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. Neuron 60:683–697

Stefan K, Wycislo M, Gentner R, Schramm A, Naumann M, Reiners K, Classen J (2006) Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training. Cereb Cortex 16:376–385

Stellwagen D, Malenka RC (2006) Synaptic scaling mediated by glial TNF-alpha. Nature 440:1054–1059

Steriade M, Contreras D, Curro Dossi R, Nunez A (1993a) The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. J Neurosci 13:3284–3299

Steriade M, Nunez A, Amzica F (1993b) Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci 13:3266–3283

Steriade M, Nunez A, Amzica F (1993c) A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci 13:3252–3265

Steriade M, Timofeev I, Grenier F (2001) Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol 85:1969–1985

Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, Brown RE, Strecker RE (2006) Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. Eur J Neurosci 23:2739–2748

Terao A, Steininger TL, Hyder K, Apte-Deshpande A, Ding J, Rishipathak D, Davis RW, Heller HC, Kilduff TS (2003) Differential increase in the expression of heat shock protein family members during sleep deprivation and during sleep. Neuroscience 116:187–200

Timofeev I, Grenier F, Bazhenov M, Sejnowski TJ, Steriade M (2000) Origin of slow cortical oscillations in deafferented cortical slabs. Cereb Cortex 10:1185–1199

Tobler I (2005) Phylogeny of sleep regulation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W. B. Saunders, Philadelphia

Tobler I, Borbely AA (1986) Sleep EEG in the rat as a function of prior waking. Electroencephalogr Clin Neurophysiol 64:74–76

Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150

Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62

Tononi G, Cirelli C (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81:12–34

Turner TH, Drummond SP, Salamat JS, Brown GG (2007) Effects of 42 h of total sleep deprivation on component processes of verbal working memory. Neuropsychology 21:787–795

Turrigiano GG (1999) Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. Trends Neurosci 22:221–227

Turrigiano GG (2008) The self-tuning neuron: synaptic scaling of excitatory synapses. Cell 135:422–435

Uschakov A, Grivel J, Cvetkovic-Lopes V, Bayer L, Bernheim L, Jones BE, Muhlethaler M, Serafin M (2011) Sleep-deprivation regulates alpha-2 adrenergic responses of rat hypocretin/orexin neurons. PLoS One 6:e16672

Van Dongen HP, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26:117–126

Varshavsky A (2012) Augmented generation of protein fragments during wakefulness as the molecular cause of sleep: a hypothesis. Protein Sci 21:1634–1661

Verkhratsky A, Petersen OH (2002) The endoplasmic reticulum as an integrating signalling organelle: from neuronal signalling to neuronal death. Eur J Pharmacol 447:141–154

Verzeano M, Negishi K (1960) Neuronal activity in cortical and thalamic networks. J Gen Physiol 43(6)Suppl:177–195

Volgushev M, Chauvette S, Mukovski M, Timofeev I (2006) Precise long-range synchronization of activity and silence in neocortical neurons during slow-wave oscillations [corrected]. J Neurosci 26:5665–5672

Vyazovskiy V, Achermann P, Borbely AA, Tobler I (2004a) Interhemispheric coherence of the sleep electroencephalogram in mice with congenital callosal dysgenesis. Neuroscience 124:481–488

Vyazovskiy V, Borbely AA, Tobler I (2000) Unilateral vibrissae stimulation during waking induces interhemispheric EEG asymmetry during subsequent sleep in the rat. J Sleep Res 9:367–371
Vyazovskiy VV (2013) Cortical neuronal mechanisms of sleep homeostasis. Zh Vyssh Nerv Deiat Im I P Pavlova 63:13–23
Vyazovskiy VV, Achermann P, Borbely AA, Tobler I (2004b) The dynamics of spindles and EEG slow-wave activity in NREM sleep in mice. Arch Ital Biol 142:511–523
Vyazovskiy VV, Achermann P, Tobler I (2007a) Sleep homeostasis in the rat in the light and dark period. Brain Res Bull 74:37–44
Vyazovskiy VV, Borbely AA, Tobler I (2002a) Interhemispheric sleep EEG asymmetry in the rat is enhanced by sleep deprivation. J Neurophysiol 88:2280–2286
Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008a) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11:200–208
Vyazovskiy VV, Cirelli C, Tononi G (2011a) Electrophysiological correlates of sleep homeostasis in freely behaving rats. Prog Brain Res 193:17–38
Vyazovskiy VV, Cirelli C, Tononi G, Tobler I (2008b) Cortical metabolic rates as measured by 2-deoxyglucose-uptake are increased after waking and decreased after sleep in mice. Brain Res Bull 75:591–597
Vyazovskiy VV, Deboer T, Rudy B, Lau D, Borbely AA, Tobler I (2002b) Sleep EEG in mice that are deficient in the potassium channel subunit K.v.3.2. Brain Res 947:204–211
Vyazovskiy VV, Faraguna U, Cirelli C, Tononi G (2009a) Triggering slow waves during NREM sleep in the rat by intracortical electrical stimulation: effects of sleep/wake history and background activity. J Neurophysiol 101:1921–1931
Vyazovskiy VV, Harris KD (2013) Sleep and the single neuron: the role of global slow oscillations in individual cell rest. Nat Rev Neurosci 14:443–451
Vyazovskiy VV, Olcese U, Cirelli C, Tononi G (2013) Prolonged wakefulness alters neuronal responsiveness to local electrical stimulation of the neocortex in awake rats. J Sleep Res 22: 239–250
Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G (2011b) Local sleep in awake rats. Nature 472:443–447
Vyazovskiy VV, Olcese U, Lazimy YM, Faraguna U, Esser SK, Williams JC, Cirelli C, Tononi G (2009b) Cortical firing and sleep homeostasis. Neuron 63:865–878
Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G (2007b) Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. Sleep 30:1631–1642
Vyazovskiy VV, Ruijgrok G, Deboer T, Tobler I (2006) Running wheel accessibility affects the regional electroencephalogram during sleep in mice. Cereb Cortex 16:328–336
Vyazovskiy VV, Tobler I (2005) Regional differences in NREM sleep slow-wave activity in mice with congenital callosal dysgenesis. J Sleep Res 14:299–304
Vyazovskiy VV, Tobler I (2008) Handedness leads to interhemispheric EEG asymmetry during sleep in the rat. J Neurophysiol 99:969–975
Vyazovskiy VV, Tobler I (2012) The temporal structure of behaviour and sleep homeostasis. PLoS One 7:e50677
Vyazovskiy VV, Tobler I, Winsky-Sommerer R (2007c) Alteration of behavior in mice by muscimol is associated with regional electroencephalogram synchronization. Neuroscience 147:833–841
Vyazovskiy VV, Welker E, Fritschy JM, Tobler I (2004c) Regional pattern of metabolic activation is reflected in the sleep EEG after sleep deprivation combined with unilateral whisker stimulation in mice. Eur J Neurosci 20:1363–1370
Walter P, Ron D (2011) The unfolded protein response: from stress pathway to homeostatic regulation. Science 334:1081–1086
Werth E, Achermann P, Borbely AA (1996) Brain topography of the human sleep EEG: antero–posterior shifts of spectral power. NeuroReport 8:123–127

Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006) Learning induces long-term potentiation in the hippocampus. Science 313:1093–1097

Winters BD, Huang YH, Dong Y, Krueger JM (2011) Sleep loss alters synaptic and intrinsic neuronal properties in mouse prefrontal cortex. Brain Res 1420:1–7

Xue X, Piao JH, Nakajima A, Sakon-Komazawa S, Kojima Y, Mori K, Yagita H, Okumura K, Harding H, Nakano H (2005) Tumor necrosis factor alpha (TNFalpha) induces the unfolded protein response (UPR) in a reactive oxygen species (ROS)-dependent fashion, and the UPR counteracts ROS accumulation by TNFalpha. J Biol Chem 280:33917–33925

Yang G, Gan WB (2012) Sleep contributes to dendritic spine formation and elimination in the developing mouse somatosensory cortex. Dev Neurobiol 72:1391–1398

Yokoyama TK, Mochimaru D, Murata K, Manabe H, Kobayakawa K, Kobayakawa R, Sakano H, Mori K, Yamaguchi M (2011) Elimination of adult-born neurons in the olfactory bulb is promoted during the postprandial period. Neuron 71:883–897

Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP (2007) A deficit in the ability to form new human memories without sleep. Nat Neurosci 10:385–392

Zavada A, Strijkstra AM, Boerema AS, Daan S, Beersma DG (2009) Evidence for differential human slow-wave activity regulation across the brain. J Sleep Res 18:3–10

Ziemann U (2004) LTP-like plasticity in human motor cortex. Suppl Clin Neurophysiol 57:702–707

Sleep and Synaptic Plasticity in the Developing and Adult Brain

Marcos G. Frank

Abstract Sleep is hypothesized to play an integral role in brain plasticity. This has traditionally been investigated using behavioral assays. In the last 10–15 years, studies combining sleep measurements with in vitro and in vivo models of synaptic plasticity have provided exciting new insights into how sleep alters synaptic strength. In addition, new theories have been proposed that integrate older ideas about sleep function and recent discoveries in the field of synaptic plasticity. There remain, however, important challenges and unanswered questions. For example, sleep does not appear to have a single effect on synaptic strength. An unbiased review of the literature indicates that the effects of sleep vary widely depending on ontogenetic stage, the type of waking experience (or stimulation protocols) that precede sleep and the type of neuronal synapse under examination. In this review, I discuss these key findings in the context of current theories that posit different roles for sleep in synaptic plasticity.

Keywords Hebbian · Synaptic scaling · Homeostasis · Function · Ontogeny · Synaptic remodeling

Contents

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1 Introduction

Sleep has long been suspected to play important roles in brain plasticity. Historically, scientists conceptualized and investigated the problem in terms of what was known about long-term synaptic potentiation (LTP) and depression (LTD) [reviewed in (Benington and Frank 2003; Frank and Benington 2006)]. LTP and LTD refer to use-dependent, persistent alterations in synaptic weights that strengthen (LTP) or weaken (LTD) specific synapses, respectively (Malenka and Bear 2004). These forms of plasticity are considered Hebbian because they are associative, input (synapse) specific, and require coordinated pre and postsynaptic activity (Markram et al. 2011). Although these effects were originally identified in vitro and involved what were at the time considered nonphysiological stimulus protocols, LTP and LTD can be induced and may occur naturally in vivo. These and related forms of synaptic plasticity are now widely considered to be cellular correlates (if not the substrates) of memory (Bear and Malenka 1994; Malenka and Bear 2004; Markram et al. 2011).

In the late 1990s, a non-Hebbian type of plasticity was described that adjusted all synapses in a neuron or network of neurons upward or downward in response to global changes in activity. This type of plasticity was dubbed "synaptic scaling" or "homeostatic synaptic plasticity" (Pozo and Goda 2010; Turrigiano 1999, 2008) and was proposed to offset pure Hebbian mechanisms in the brain. In the following sections, I discuss our current knowledge concerning the potential role of sleep in both Hebbian and non-Hebbian synaptic plasticity in the developing and adult brain. I also discuss these findings in the context of recent theories of sleep function that incorporate Hebbian and non-Hebbian forms of plasticity in different ways.

2 Sleep and Developmental Plasticity

In most of the mammalian species studied in detail, sleep amounts are highest during the neonatal period, the phase of life that is characterized by rapid brain development and synaptic plasticity (Frank and Heller 1997; Jouvet-Mounier et al.

1970; Roffwarg et al. 1966). Therefore, if sleep contributes to synaptic plasticity one would expect this to be especially true in developing animals. This possibility has been investigated in the visual system which is highly plastic during a *critical period* of development. The critical period refers to a developmental window of time when the brain is exquisitely sensitive to changes in experience. It has been traditionally investigated by closing an eye [monocular deprivation (MD)], which alters cortical responses in favor of the open eye [reviewed in (Sengpiel et al. 1998; Singer 1979)]. These changes in vivo are temporally associated with a form of an in vitro cortical LTP. In this type of LTP, high frequency white matter stimulation in cortical slices prepared from postnatal (P) day 28–30 rats produces synaptic potentiation in cortical layers II/III. This form of LTP is not observed in cortical slices from adult rats (Kirkwood et al. 1995). In the last decade, several in vitro and in vivo studies suggest an important role for sleep in these types of plasticity [for additional discussion, see (Frank 2011)].

2.1 Sleep and Developmentally Regulated LTP In Vitro

While both nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep may play a role in synaptic plasticity, REM sleep in particular may be important for developmentally regulated plasticity. Studies in rats show that 1 week of REM sleep deprivation prolongs the critical period for the developmentally regulated form of LTP in vitro (Shaffery et al. 2002). That is, after REM sleep deprivation, LTP can be induced at ages when this form of plasticity is normally no longer present. A similar extension of the critical period was not seen in cortical slices from control rats. Conversely, REM sleep deprivation had no effect on a nondevelopmentally regulated form of LTP evoked by layer IV stimulation. Subsequent studies from these investigators showed that this plasticity could be partially rescued if REM sleep deprivation was administered near (or overlapping) the end of the critical period (Shaffery et al. 2005; Shaffery and Roffwarg 2003). More recent findings show that the effects of REM sleep deprivation can be prevented by chronically infusing brain-derived neurotrophic factor (BDNF) into the visual cortex. This indicates that REM sleep may normally promote BDNF synthesis (Shaffery et al. 2012). This idea is supported by work in the developing cat, demonstrating that sleep is accompanied by increased cortical synthesis of BDNF (Seibt et al. 2012).

2.2 Sleep and Ocular Dominance Plasticity (ODP)

ODP refers to electrophysiological and anatomical changes in visual cortical circuits in vivo triggered by MD or other changes in patterned vision. These changes include a shift in evoked electrical potentials and an expansion of thalamocortical

efferent axonal arbors in favor of the seeing eye. Although originally described in developing animals (Hubel and Wiesel 1970; Wesel and Hubel 1963), ODP also occurs in the adult brain (Sato and Stryker 2008; Sawtell et al. 2003) and shares in common numerous mechanisms that mediate Hebbian and non-Hebbian plasticity in the hippocampus and nonsensory cortex. ODP is considered *physiological* for the following reasons. First, it occurs in the intact, unanesthetized brain in response to changes in sensory input that animals actually experience. Second, while the experimental procedure of MD is artificial, as is the case for many laboratory manipulations, this change in visual input occurs naturally in amblyopia. Amblyopia occurs in humans (and other mammals with binocular vision) when patterned vision is reduced in one eye during early life, often as a result of a cataract. Third, the resulting plasticity involves naturally occurring changes in synaptic proteins and molecules. Fourth, the underlying plasticity is present, with or without MD, as it governs cortical adjustments to visual input that normally occur during the critical period. For these reasons, ODP is recognized as a canonical model of physiological plasticity in vivo [for review see, (Espinosa and Stryker 2012; Tropea et al. 2009)].

A role for sleep in ODP has been demonstrated in the cat. During the peak of the critical period, as little as 6 h of sleep significantly enhances the effects of MD on cortical neurons; a process which does not occur when animals are instead sleep-deprived (Frank et al. 2001). Subsequent investigations have shown that this form of sleep-dependent plasticity requires cortical neuronal activity (Frank et al. 2006; Jha et al. 2005). For example, after MD reversible inactivation of the sleeping visual cortex with gamma-aminobutyric acid (GABA) receptor agonists or the cation channel blocker lidocaine inhibits the enhancement of ODP normally observed after sleep. These results were not due to abnormal sleep or visual processing upon testing—as sleep architecture and basic visual response properties were unchanged in infused animals. Interestingly, additional sleep with cortical activity restored did not rescue ODP. This indicates that sleep immediately following waking experience is critical for the consolidation of this type of plasticity (Jha et al. 2005).

Although the precise activity-dependent mechanisms engaged in the sleeping brain are unknown, they include synaptic potentiation. For example, both acute (Aton et al. 2009) and chronic recording (Aton et al. 2013) of single neurons show that responses to the nondeprived eye become stronger after sleep. In comparison, sleep has little to no effect on the magnitude of depression observed in the deprived-eye pathway. Infusing NMDAR antagonists, protein kinase inhibitors, or blocking protein synthesis (Fig. 1) in the visual cortex during post-MD sleep completely abolishes this potentiated response (Aton et al. 2009; Seibt et al. 2012). In addition, post-MD sleep is accompanied by activation of several kinases implicated in LTP [extracellular regulated kinase [ERK] and calcium calmodulin kinase II (CaMKII)] and phosphorylation of glutamate AMPA receptors (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 of several proteins implicated in LTP [e.g., BDNF and postsynaptic density (PSD)-95] (Seibt et al. 2012).

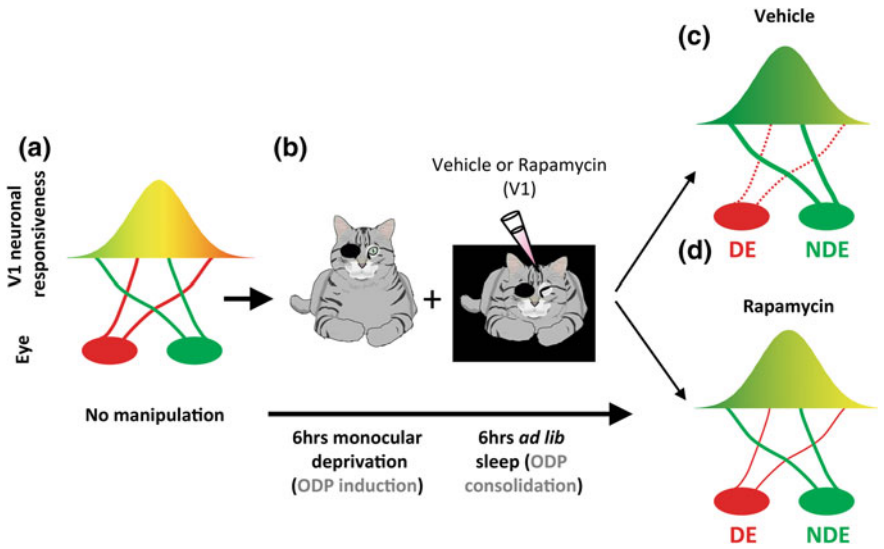

Fig. 1 Ocular dominance plasticity in the cat requires protein synthesis during sleep. **a** In developing cats with normal vision, most neurons in the primary visual cortex (V1) are binocular (i.e., equally responsive to inputs from either eye, represented as the *yellow* area). **b** When animals are deprived of patterned visual input in one eye (i.e., monocular deprivation) most neurons in V1 become responsive only to stimulation of the nondeprived eye (NDE). This canonical form of physiological plasticity is known as ocular dominance plasticity (ODP). It is induced very rapidly in awake cats (6 h) and is enhanced/consolidated by subsequent sleep (6 h). To test the role of protein synthesis in sleep-dependent ODP, visual cortices are infused with vehicle or the selective mammalian target of rapamycin (mTOR) inhibitor during the post-MD sleep period. **c** Sleep-dependent ODP is intact in the vehicle infused hemispheres and includes a maintenance of depression of the DE visual input (*dotted red line*) and potentiation of the NDE input (*thick red line*). **d** Inhibition of protein synthesis in V1 with rapamycin during post-MD sleep blocks sleep-dependent ODP. This essentially halts plastic changes at a stage induced by waking experience alone. Reproduced with permission from (Seibt and Frank 2012)

A particular striking set of observations in the cat is that plasticity in wakefulness and sleep appear to be governed by distinct mechanisms. In addition to a difference in the direction of plastic change (weakening in wakefulness, strengthening in sleep), the effects of MD in the awake brain do not require protein synthesis. In contrast to sleep-dependent plasticity, intracortical blockade of protein synthesis has no effect on circuit weakening in wakefulness. In addition, while a number of plasticity-related mRNAs are upregulated by visual experience, they are not translated into proteins until sleep occurs (Seibt et al. 2012). This suggests that the transcription and translation of plasticity-related mRNAs are divided across sleep and wake (Fig. 2).

A two-stage process in ODP is further demonstrated by a recent study of single neuron activity in freely behaving animals. Aton et al. (2013) used chronic, stereotrode recording of single visual cortical neurons to track their activity and interactions before, during, and after a period of MD. In contrast to previous

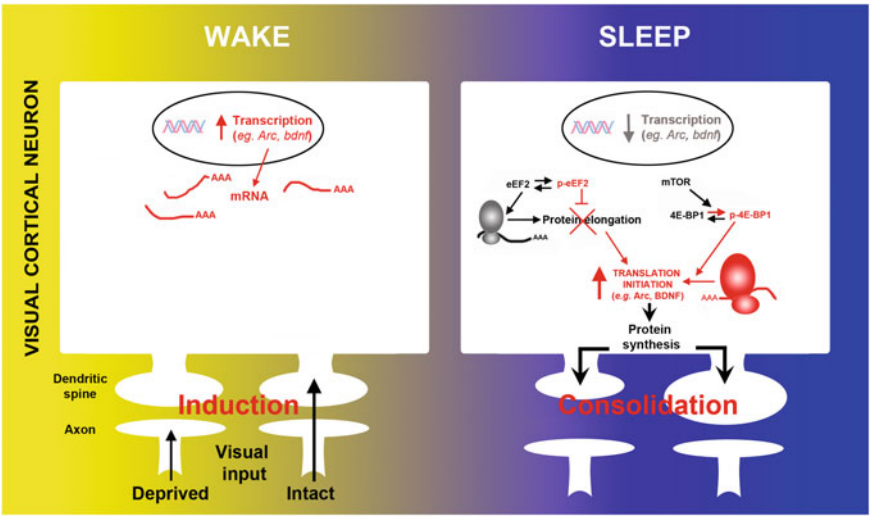

Fig. 2 The transcription and translation of plasticity-related mRNAs are divided across wake and sleep. During wake, monocular deprivation triggers activity-dependent transcription of immediate-early and neurotrophin genes (e.g., *arc*, *bdnf, c-fos*) in V1. Subsequent sleep activates a cascade of translational events (increased translation initiation via 4E-BP1 phosphorylation and reduced global elongation via eEF2 phosphorylation) leading to a net increase in translation initiation of subsets of mRNA. *Arc* and *bdnf* are two examples of important plasticity-related genes where transcription is decreased and translation is increased during sleep. Reproduced with permission from (Seibt et al. 2012)

studies employing similar longitudinal recording (Mioche and Singer 1989), neuronal activity was also recorded across the sleep-wake cycle. MD in the awake animal caused a profound reduction in firing rate in fast-spiking neurons (i.e., putative GABAergic cells) in the visual cortex. This decrease in activity was maintained during the first 6 h of post-MD sleep and accompanied by an increase in firing in regular-spiking neurons (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. Together, these results clearly demonstrate that sleep promotes cortical potentiation in the developing cat cortex.

The above results cannot be ascribed to nonphysiological processes resulting from MD as recently asserted (Tononi and Cirelli 2014). For example, it was claimed that the effect of short-term MD used in these studies (6 h) is nonphysiological because "wake is accompanied not by the usual net potentiation but by massive synaptic depression" (Tononi and Cirelli 2014). This is incorrect in three aspects. First, there is no "massive" synaptic depression after only 6 h of MD (Aton et al. 2009; Dumoulin et al. 2013; Frank et al. 2001; Seibt et al. 2012). Several *days* of MD in cats are required to produce what might constitute "massive" (i.e., saturating) weakening effects in deprived eye pathways (Crair et al. 1997; Olson and

Freeman 1975, 1980). However, 6 h of MD in the awake cat only produces a small change in these circuits. Second, there are many examples of waking experience that do not produce "net potentiation", but instead synaptic weakening [for discussion, see (Frank 2012)]. While it is true that motor learning commonly leads to potentiation in motor cortex, this is not universally true in other parts of the brain or with other types of experience (Frank 2012). Therefore, the mere direction of plastic change does not determine whether the underlying plasticity is "nonphysiological". Third, although MD eventually leads to large changes in thalamocortical circuitry, other manipulations of experience in early life do so as well (de Villers-Sidani and Merzenich 2011; Foeller and Feldman 2004). The fact that the developing brain is more plastic than the adult brain does not mean that developmental plasticity is "nonphysiological". It was further claimed that short-term MD is "followed by a 40 % decrease in slow waves during subsequent sleep" (Miyamoto et al. 2003). The 40 % reduction in NREM slow wave activity (SWA) in the Miyamoto study was *not* induced by MD, but by months of dark rearing from birth (Miyamoto et al. 2003), which is a completely different experimental paradigm with very different effects on developing circuits (Buisseret and Imbert 1976; Fagiolini et al. 1994). In fact, short-term MD used in studies from the Stryker and Frank laboratories does not significantly reduce visual cortical SWA (Seibt et al. 2012) or alter in any way basic visual processing in cortical neurons, except the expected loss of response to the deprived eye. More specifically, visual responses in the intact visual pathway are completely normal, which is to be expected if the underlying processes are physiological (Frank et al. 2001). In addition, the blockade of ODP by sleep deprivation is unlikely explained by increases in stress hormone concentration. This is because ODP is remarkably resistant to the effects of the principal stress hormone corticosterone (Daw et al. 1991), and corticosterone levels after MD (or sleep deprivation) are tenfold lower than those reported to reduce ODP (unpublished observations).

3 Sleep and Plasticity in the Adult Brain

3.1 LTP and LTD: In Vitro and In Vivo Studies in Adult Animals

The role of sleep in adult synaptic plasticity has historically been investigated using classic Hebbian LTP and LTD. Beginning in the late 1980s, several investigators showed that sleep states influence tetany-induced LTP in animal models [reviewed in (Benington and Frank 2003; Hennevin et al. 2007)]. Overall, it appears that hippocampal LTP can be induced during REM sleep, whereas similar stimulus protocols during NREM sleep have no effect or produce LTD. Subsequent investigations have shown that sleep and sleep loss can affect the induction or maintenance of LTP in vivo and in vitro. Romcy-Pereira and Pavlides (Romcy-Pereira and Pavlides 2004) found that REM sleep deprivation and total

sleep deprivation impair the maintenance of LTP in the dentate gyrus, but enhance this process in the medial prefrontal cortex (mPFC). Marks and Wayner found that sleep disruption also reduces hippocampal LTP in anesthetized rats (Marks and Wayner 2005). Kim et al., also employed the "flower pot" REM sleep deprivation technique for 5 days in rats, after which tetany was applied to the hippocampus while the animals were awake (Kim et al. 2005). In contrast to Marks and Wayner, these investigators report a delayed effect of REM sleep deprivation on LTP; reductions in LTP were observed 24 h after the termination of REM sleep deprivation. A large number of studies also show that in vitro hippocampal LTP (either the incidence or maintenance) is reduced in rodents that undergo varying amounts of REM sleep deprivation, total sleep deprivation, or sleep restriction (Arrigoni et al. 2009; Campbell et al. 2002; Chen et al. 2006; Davis et al. 2003; Florian et al. 2011; Ishikawa et al. 2006; Kopp et al. 2006; McDermott et al. 2003, 2006; Ravassard et al. 2006, 2009; Tartar et al. 2006; Vecsey et al. 2009).

The underlying mechanisms mediating the effects of sleep loss on LTP and LTD are not well understood. However, they do not appear to 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). Diminished plasticity may instead be linked to decrements in hippocampal NMDA receptor function (Chen et al. 2006; Kopp et al. 2006; Longordo et al. 2009; McDermott et al. 2005) and ERK/MAPK activation (Ravassard et al. 2009) combined with reductions in plasticity-related mRNAs or proteins (Davis et al. 2006; Guzman-Marin et al. 2006), and elevated concentrations of PDE4 (Vecsey et al. 2009) and extracellular adenosine (Arrigoni et al. 2009; Florian et al. 2011).

Most studies of LTP and sleep have focused on the adult hippocampus. Consequently, very little is known about how sleep and sleep loss impact adult cortical plasticity. Aton et al., provide some of the first unequivocal evidence that sleep directly promotes naturally occurring LTP in the adult cortex in vivo (Aton et al. 2014). In adult nonanesthetized mice, brief exposure to a visual stimulus (phase-reversing, oriented gratings) results in an enhancement of cortical responses to stimuli of the same orientation (orientation-specific response potentiation: OSRP). OSRP is considered an in vivo form of LTP because it involves many of the same mechanisms governing Hebbian LTP in vitro (Cooke and Bear 2010). For example, tetany-induced cortical LTP occludes subsequent OSRP (and vice versa). Occlusion is a classic means of determining if two processes share the same intracellular mechanisms. Occlusion occurs because one process depletes substrates (e.g., phosphorylated proteins) that are also used for the second process. The role of sleep in adult OSRP was investigated by examining the effects of experience alone, or in combination with a subsequent period of sleep, or sleep deprivation. Chronic stereotrodes were used to chronically record the activity of single cortical neurons in the visual cortex in unanesthetized adult mice before, during, and after presentation of a specifically orientated grating (the training stimulus). OSRP developed several hours after the stimulus presentation, but only after the mice slept. OSRP was prevented when the animals were instead kept awake after the stimulus (Aton et al. 2014).

3.2 Replay-Reactivation of Waking Experience in the Sleeping Adult Brain

In the mid-1990s, Matt Wilson and Bruce McNaughton demonstrated that hippocampal place cells in rats replay patterns of activity during sleep originally present during prior waking experience (Wilson and McNaughton 1994). This work extended previous findings from Pavlides and Winson (1989), who found that place cells active during exploration showed increased activity in subsequent sleep. Collectively, these findings led to the theory that replay may be a means of transferring information (or memories) from the hippocampus to the neocortex (Buzsaki 1996; Diekelmann and Born 2010). On a synaptic level, this transfer likely involves LTP as it occurs during rapid bursts of hippocampal activity among specific sets of circuits [ripples and sharp waves] (Buzsaki 1996; Schwindel and McNaughton 2011). Evidence of replay has been found in an impressive number of animal species, ranging from birds (Dave and Margoliash 2000) to primates(Hoffman and McNaughton 2002) and based on brain imaging, humans (Deuker et al. 2013; Maquet et al. 2000; Peigneux et al. 2004). The animal studies are also embedded in well-established paradigms of behavior, cellular physiology, and plasticity [reviewed in (Girardeau and Zugaro 2011; Schwindel and McNaughton 2011)].

The phenomenon appears quite robust, as variants have been found in the rodent hippocampus, ventral striatum, and cortex (Ji and Wilson 2007; Kudrimoti et al. 1999; Lee and Wilson 2002; Louie and Wilson 2001; Pennartz et al. 2004; Skaggs and McNaughton 1996; Wilson and McNaughton 1994). Although there is some evidence that forms of replay occur during REM sleep (Louie and Wilson 2001; Poe et al. 2000), communication between the hippocampus and cortex is generally conjectured to occur during NREM sleep. This is because during this state activity in the hippocampus is consistent with outflow, rather than inflow (Buzsaki 1996; Diekelmann and Born 2010; Graves et al. 2001; Hasselmo 1999). There are indeed interesting correlations between ripples and sharp waves (hippocampal events when replay is reported) and thalamocortical spindles and delta waves consistent with this hypothesis (Battaglia et al. 2004; Siapas and Wilson 1998; Sirota et al. 2003). In addition, though quite rare, there are instances when hippocampal and cortical replay occur simultaneously (Ji and Wilson 2007; Qin et al. 1997).

3.3 Re-examining Replay-Reactivation

To summarize, there is little doubt about the presence of neuronal replay during sleep. The basic findings of Wilson and McNaughton have been replicated and extended in the rodent model and similar forms of reactivation are reported in other vertebrates including, possibly, humans. Historically, however, there has been some doubt about the significance of neuronal replay.

First, replay is not unique to sleep. Replay can be detected during periods of waking immobility and even during active exploration (Foster and Wilson 2006; Kudrimoti et al. 1999; O'Neill et al. 2006). This in turn suggests that replay may have little to do with central functions of sleep and is instead one of many phenomena that are peripherally modulated by sleep. While it remains possible that replay in sleep is qualitatively different than replay in wake, this has yet to be fully determined. Therefore sleep is sufficient but not necessary for replay.

Second, replay in sleep is generally not detected during learning but well after the animal learns the task. For example, most studies require that the animals be pretrained on a maze for several days to weeks before replay can be detected (Frank 2007; Peyrache et al. 2009). The slow appearance of replay might reflect a gradually developing engram that appears after initial learning and contributes to the transfer of memories from short-term stores (hippocampus) to long-term stores (neocortex). However, it could also indicate that replay is only a decaying reverberation of a very well-ingrained pattern of neural activity present during wakefulness. This may explain the ephemeral nature of replay. It is typically detectable only within the first 20–30 min of sleep and then fades away. In some measures, it also accounts for only a fraction of total variance in neuronal activity [reviewed in (Frank 2007)].

Unfortunately, very little data exist on the effects of novel experience on replay which might distinguish between these two possibilities. Some studies do show that neuronal activity patterns associated with novel maze running or motor behavior can be detected in sleep within a few days (as opposed to weeks for familiar mazes), but the novel tasks are often very similar to familiar tasks. For example, in one study there was substantial overlap in cells active in the familiar versus novel maze configurations [between 70 and 77 % (Kudrimoti et al. 1999)]. This issue seemed to be resolved by studies reporting novelty induced reactivation of waking activity patterns in the sleeping rat forebrain (Ribeiro 2004, 2007), but these findings have been challenged on technical and methodological grounds (Tatsuno et al. 2006). Recent findings from Peyrache et al., however, provide more compelling evidence that replay can occur following novel experience. In this study, rats were exposed to novel learning rules, and medial prefrontal cortex ensemble recordings showed that patterns of activity induced by learning "replayed" in subsequent NREM sleep (Peyrache et al. 2009).

A final consideration is that until quite recently, there has been no convincing evidence that replay in sleep has any function. Two independent studies in rodents provide evidence that interrupting the hippocampal bursts that convey replay impairs critically important behavior [learning and memory] (Ego-Stengel and Wilson 2010; Girardeau et al. 2009). These studies must be cautiously interpreted because they involved disruption of the hippocampal ripples and sharp waves, and not replay per se. It is also not clear if similar results would obtain if disruption were restricted to replay in wakefulness versus sleep. More recently, it has been shown that hippocampal replay during sleep can be triggered by presentation of auditory tones present during experience—which suggests that replay represents a memory trace (Bendor and Wilson 2012). 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.

3.4 The Synaptic Homeostasis Hypothesis

Numerous theories have been proposed to explain how sleep may influence synaptic plasticity in the adult brain. In the last decade, SHY has received particular attention. Its hypothesized roles for sleep are not unique. Several theories proposing a synaptic weakening effect in either NREM or REM sleep predate SHY (Crick and Mitchison 1983, 1995; Giuditta 1995). Other scientists have also proposed mechanisms by which synapses might be weakened in sleep (Benington and Frank 2003; Poe et al. 2000). SHY, however, encompasses a number of perennial ideas about sleep function in one theory (e.g., metabolism, plasticity and homeostasis). It also attempts to integrate Hebbian and non-Hebbian forms of plasticity across the sleep-wake cycle.

In the original description of SHY, learning occurs during wakefulness through synaptic potentiation which in turn drives sleep need. This form of synaptic potentiation appeared to be Hebbian LTP. First of all, it was described interchangeably as "long-term potentiation," "LTP," and "LTP-like" (Tononi and Cirelli 2003, 2006). The former terms classically refer to Hebbian mechanisms (Markram et al. 2011). Second, the synaptic potentiation of wakefulness involved "strong presynaptic firing…accompanied by postsynaptic depolarization" (Tononi and Cirelli 2006), which is a hallmark of correlation-based, or Hebbian LTP (Markram et al. 2011).

According to SHY, sleep weakens synapses through a process originally called downscaling (Tononi and Cirelli 2003, 2006), and more recently renamed as "synaptic renormalization" (Tononi and Cirelli 2012). The mechanisms governing renormalization are unspecified. However, the core features of synaptic renormalization are very similar to forms of non-Hebbian plasticity identified in the late 1990s. As originally described by Turrigiano et al. (1998), *synaptic scaling* (or *homeostasis*) is characterized by a global adjustment of synaptic weights in a neuron or network which is proportional to the strength at each synapse. Synaptic downscaling is proposed to offset Hebbian LTP, which if left unchecked would result in run-away synaptic strengthening that would saturate a neuron or neuronal network's ability to form new synapses, or further strengthen existing ones (Turrigiano 1999, 2007; Turrigiano et al. 1998; Turrigiano and Nelson 2000). Therefore, the key concept of synaptic scaling is a global adjustment of synaptic weights that allows the network to retain past information, make new connections, and avoid network instability (i.e., a saturation of synaptic strength).

Synaptic renormalization has the same basic properties. In SHY, downscaling (or "renormalization"), affects all or most synapses, it offsets LTP (or LTP-like

plasticity), and thereby allows more potentiation to occur (i.e., more learning). It involves a form of synaptic weakening (originally called "downscaling") that is also 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, as sleep prevents "synaptic overload" (Tononi and Cirelli 2006). There appear to be only two principle differences between synaptic scaling proper and synaptic renormalization. First, in SHY LTP (or LTP-like plasticity) and downscaling are divided across wakefulness and sleep, respectively. Second, the cellular mechanisms governing synaptic scaling are not integrated into SHY. There are additional components to SHY not explicitly discussed in the original descriptions of synaptic scaling (e.g., metabolism, "synaptic space"). These, however, represent relatively minor differences or an emphasis on different outcomes of the same basic process.

3.5 Re-examining SHY

The theoretical underpinnings and evidence for SHY have been extensively reviewed elsewhere (Frank 2012; Tononi and Cirelli 2014). There is little doubt that under certain conditions and within some brain regions, synapses appear to be weaker after prolonged sleep periods. These findings are consistent with SHY and other theories that posit a similar synaptic weakening effect of sleep (Crick and Mitchison 1983; Giuditta 1995). Very little is known, however, about the mechanisms that drive this weakening process and whether they truly require sleep (Frank 2012, 2013).

For example, a central role was originally given to NREM slow wave activity (SWA), which was proposed to directly downscale synapses (Tononi and Cirelli 2003, 2006). This role has become obscure over the years, as SWA is sometimes also considered an "index" (Tononi 2009) or "sensor" of synaptic potentiation (Tononi and Cirelli 2012). Regardless of the particular role ascribed to SWA in SHY, there is currently no direct evidence that SWA in vivo weakens synapses (Frank 2012; Steriade and Timofeev 2003), and some findings indicating quite the opposite. For example, Tsanov and Manahan-Vaughan showed that when measured during the rodent light phase (when rodents sleep), evoked cortical excitatory postsynaptic potentials (EPSPs) do not decline across the sleep period, and peaks in SWA precede increases in EPSPs. These results suggest that in the adult visual cortex, sleep and possibly SWA, might promote synaptic strengthening. This is consistent with Tsanov and Manahan-Vaughan's own conclusions, i.e., that the light (sleep) phase "…leads to synaptic potentiation" (Tsanov and Manahan-Vaughan 2007).

More direct evidence that SWA promotes synaptic potentiation comes from Chauvette et al. (2012) who showed that cortical postsynaptic potentials in vivo are potentiated after a period of NREM SWA, but not wakefulness. They also showed that periods of wakefulness did not result in synaptic potentiation. Intriguingly, experiments in vitro which simulated SWA specifically led to

synaptic potentiation, while simulations of waking activity did not. It has been suggested that this is due to sleep inertia in the waking periods following sleep (Tononi and Cirelli 2014), but this is unlikely for several reasons. First, there were no significant differences in membrane potential in wake before or after NREM sleep (Timofeev personal communication). Second, the initial enhancement of the electrophysiological response persisted over several sleep-wake cycles, which would be unlikely if this was due to a transient inertial effect. Third, sleep inertia cannot explain the results of the experiments in vitro where membrane potential was controlled (Chauvette et al. 2012).

It also appears that synaptic scaling, as presently understood, does not operate in a manner consistent with SHY. As discussed above, the concepts of synaptic scaling are incorporated to a large degree into SHY. It is therefore reasonable to ask whether mechanisms known to govern synaptic downscaling might also govern "synaptic renormalization" in sleep. As recently reviewed (Frank 2012), many molecular and electrophysiological changes reported across the sleep-wake cycle are inconsistent with *only* global synaptic downscaling during sleep. For example, it has been suggested that global decreases in cortical activity (down-states) that occur during NREM sleep might downscale synapses. However, the basic principle of synaptic scaling is that global decreases in neuronal activity upscale synapses, while increases in neuronal activity downscale synapses. Consequently, down-states in NREM sleep should upscale, not downscale synapses (Frank 2012).

An additional consideration is that non-Hebbian synaptic scaling might be state-independent and thus occurs without sleep (Frank 2012). This possibility is supported by findings in the visual cortex in vivo. In one study, changes in cortical firing rates were chronically recorded after manipulations known to induce non-Hebbian synaptic scaling in the monocular segment of the visual cortex. There was no evidence of state-dependent alterations in scaling; rather decreases and increases in cortical activity were similar in wake and sleep (Hengen et al. 2013). Whether downscaling and upscaling both occur equally independently of vigilance state is presently unknown. Collectively, however, the above findings do not support a unique role for sleep in synaptic homeostasis.

Given the above considerations, it is not clear if the synaptic changes reported after sleep in support of SHY reflect an active sleep-dependent mechanism. They may instead result from other physiological processes that coincide with sleep, but are themselves not sleep-dependent (Frank 2012). These include circadian rhythms in brain temperature and in mammal's glucocorticoid secretion.

3.6 Independent Factors that Alter Synapses: Brain Temperature

In mammals, the biological clock produces rhythms in brain temperature with a peak in the active phase and a trough in the sleep phase (Glotzbach and Heller 2000). Therefore, the effects of elevated brain temperature on synapses will

accumulate during the normal waking period and decline during sleep. What might these effects be? A number of studies in vitro show that cooler temperatures cause a number of synaptic changes similar to those reported after sleep. These include a reduction in dendritic spines (Roelandse and Matus 2004) and concentrations of proteins that make up the postsynaptic density (Roelandse and Matus 2004). Cooling also reversibly reduces excitatory postsynaptic field potentials (EPSPs), and reverses (de-potentiates) LTP (Bittar and Muller 1993) and reduces cortical synaptic strength as measured by mini-EPSPs (Simkus and Stricker 2002).

Strong effects of naturally occurring brain temperature gradients on EPSPs are also reported in freely behaving rodents (Moser et al. 1993). Prior to Moser's now classic studies, field recordings from the hippocampus (EPSPs) in vivo were thought to exclusively reflect plastic changes associated with learning or novel experience. They were higher after rodents engaged their environments during exploration, but not when they were less mobile. However, motor activity alone increases hippocampal temperature and EPSPs in a manner unrelated to learning-related plasticity. It is instead caused by the normal rise in brain temperature associated with waking movement and dissipates as the brain naturally cools. Similar temperature gradients across the subjective day and night have been reported in rodent cortex (Franken et al. 1991, 1993). It is also interesting that reports of heightened synaptic potentiation in wake versus sleep based on electrophysiological recordings rely on various forms of novel experience to maintain wakefulness (Hanlon et al. 2011; Vyazovskiy et al. 2008). Therefore reports of heightened cortical excitability or responsiveness in mammals after prolonged wakefulness or sleep deprivation (relative to sleep) may reflect circadian rhythms in brain temperature and secondary increases associated with motor activity—rather than vigilance state per se.

The effects of temperature may be even more extreme in insects commonly used in sleep studies. Insects are ectotherms and do not internally generate heat as do mammals. Temperature is instead behaviorally regulated either by selecting warmer environments or through activity (Stevenson 1985). Temperature gradients as small as $\approx 8^{\circ}$ C are sufficient to alter synaptic structures in *Drosophila* (Peng et al. 2007; Zhong and Wu 2004). These include increased axonal arborization in mushroom body neurons (Peng et al. 2007) and motor nerve terminals in vivo (Zhong and Wu 2004) and neurite extension in vitro (Peng et al. 2007). Intriguingly, these temperature effects are mediated by signaling pathways shared by activity-dependent synaptic plasticity [e.g., cAMP] (Peng et al. 2007). Whether similar temperature gradients exist across *Drosophila* wake and sleep is unknown, but similar gradients in ambient temperature are encountered under natural conditions (Vanin et al. 2012). They may even occur in insects housed under constant ambient temperatures. This is because core temperature tracks motor/muscle activity in small terrestrial insects (Stevenson 1985); processes which are strongly influenced by the biological clock. Interestingly, this may be especially true for flying insects which expend considerable energy to bring thoracic flight muscles to high temperatures prior to flight [a phenomenon called "pre-flight warm-up"] (Heinrich 1974). Although, as discussed by Heinrich, small flying insects *in flight*

will dissipate increases in core temperature due to convection, this may not be true under housing conditions typically used in sleep studies of *Drosophila*. Typically, *Drosophila* are housed in glass tubes that prevent flight and the convection that would occur as the animal flies through a large space. These tubes, however, do not prevent nonflight motor activity, including presumably, movements of the wings which are part of the pre-flight warm-up.

3.7 Independent Factors that Alter Synapses: Glucocorticoids

In rodents and humans, glucocorticoid (corticosterone and cortisol) concentrations rise and fall in parallel with the circadian wake and sleep phases of the 24 h day (Van Cauter 2005). They also are higher during wakefulness (relative to sleep), when waking is enforced during the normal sleep phase. There is considerable evidence that outputs of the Hypothalamic-Pituitary-Axis (HPA) profoundly influence synaptic efficacy and morphology. Glucocorticoid effects are diverse and dependent upon different classes of receptors (Joels et al. 2008). They have also been chiefly explored in the hippocampus rather than the neocortex. Nevertheless, increases in corticosterone during the normal waking period or after sleep deprivation may generally promote glutamatergic neurotransmission and neuronal excitability (Joels et al. 2008). Acute increases in corticosterone (or stress) increase the frequency (Olijslagers et al. 2008) and amplitude of mEPSCs in the hippocampus (Karst and Joels 2005), strengthen glutamatergic synapses onto dopamine neurons (Daftary et al. 2009), and increase glutamatergic release/calcium mobilization in cortical synaptoneurosomes (Satoh and Shimeki 2010). Acute increases in corticosterone also promote AMPAR synaptic transmission, AMPAR trafficking and insertion into cortical and hippocampal synapses, and cortical dendritic spine turnover (Conboy and Sandi 2009; Groc et al. 2008; Liu et al. 2010; Yuen et al. 2011). More recently it has been shown that even relatively small, transient increases in exogenous corticosterone can lead to rapid spinogenesis in vivo, which slowly decline over 5 h (Komatsuzaki et al. 2012).

Perhaps the most compelling evidence to date that normal circadian cycles of HPA activity influence cortical synaptic plasticity comes from Liston et al. (2013). In this study, it was shown that the normal peaks in glucocorticoid concentrations (during the rodent active phase) directly promote cortical dendritic spine formation that accompanies motor learning. Interestingly, they also found that the normal troughs (which correspond to the sleep phase) had dual effects; they promote the stabilization of newly formed spines associated with learning, and the pruning of preexisting spines, not associated with learning. These findings are consistent with previously reported biphasic effects of glucocorticoids which are comprised of rapid increases in synaptic efficacy (and spine formation) followed by a slower, time-dependent normalization of synapses to baseline levels [for discussion, see (Joels et al. 2008; Tse et al. 2012)]. These biphasic and prolonged synaptic changes

are strikingly similar to those ascribed to wakefulness and sleep in SHY. They are, however, ultimately driven by the biological clock and are thus not state-dependent.

4 Discussion

There has been impressive progress in our understanding of how sleep and sleep loss impact brain plasticity. There also remain a number of unresolved issues. For example, while abundant evidence exists to support a general synaptic weakening *after* sleep, it is not at all clear that these changes are caused *by* sleep. Many findings cited in support of one theory of sleep-dependent plasticity (SHY) can be explained by circadian rhythms in brain temperature and HPA activity. There is also strong evidence that under certain conditions, sleep may instead strengthen synapses. These include changes in sensory input during early life that lead to cortical re-mapping. I discuss these topics in more detail in the following sections.

4.1 Brain Plasticity in Adult and Developing Brains: Difference in Degree or Kind?

An important unanswered question is whether sleep-dependent plasticity in the developing and adult brain is different. It has been suggested, for example, that synaptic downscaling as described in SHY is even more important during early life. For example, during times of overall synaptogenesis (Tononi and Cirelli 2012). However, if these developmental ages are characterized by an overall gain of synapses (Aghajanian and Bloom 1967; Sur and Leamey 2001), and animals at these ages spend most of their time in sleep [e.g., rats $\approx$75 % (Frank and Heller 1997), ferrets (Thurber et al. 2008) $\approx$85 % total recording time], then it follows that sleep cannot be a time for net synaptic weakening. This could only be true if all the synaptogenesis is compressed into the tiny fraction of time spent awake. This seems highly unlikely. Indeed, recent work in infant rodents indicates that bursts of activity during sleep are well-suited for forming sensory/motor circuits, a process known to involve synapse formation (Khazipov et al. 2004; Tiriac et al. 2012).

It also appears that a global downscaling function for sleep cannot fully explain experience-dependent plasticity occurring at later developmental ages (Fig. 3). On the contrary, investigations into a classic, physiological form of developmental plasticity (ODP) show unequivocally that sleep potentiates responses in some circuits, while maintaining depression in others. In addition, sleep appears to play no special role in at least one type of synaptic scaling in vivo in rodents at similar ages (Hengen et al. 2013). Reconciling these findings with SHY is complicated by the fact that while progress has been made identifying the cellular mechanisms governing sleep-dependent ODP (from receptors to circuits (Frank 2011), very

little is known about the mechanisms governing SHY. It is also unclear if synaptic changes ascribed to sleep in SHY are in fact sleep-dependent (Frank 2012). Nevertheless, it remains possible that both Hebbian and non-Hebbian forms of plasticity operate during sleep in early life. For example, the effects of sleep on ODP suggest that synaptic weakening and strengthening both occur during sleep, but at different time points. The first few hours of post-MD sleep are accompanied by activation of several kinases and the synthesis of proteins implicated in LTP (Aton et al. 2009; Seibt et al. 2012). However, these events are transient, and by 6 h they return to baseline or even drop below baseline values. This is consistent with a "Boom and Bust" model shown in Fig. 3, according to which sleep first leads to synaptic potentiation, and then a general synaptic downscaling. Similar models that integrate synaptic strengthening and weakening across sleep have been proposed for the adult brain (Genzel et al. 2014; Ribeiro 2011).

One might further speculate that sleep-dependent downscaling only appears at a certain stage of development and then persists into adulthood. The appearance of this downscaling function may be tied to widespread synaptic pruning which is developmentally regulated and occurs after an earlier explosive period of synaptogenesis. Interestingly, the only age when sleep appears to eliminate dendritic spines (in mammal's) is during this one specific window of developmental time (Maret et al. 2011; Yang and Gan 2011). This particular stage of development is also closely associated with the appearance of adult-like sleep regulation and sleep architecture (Alfoldi et al. 1990; Frank et al. 1998).

4.2 Making and Breaking Synapses in Sleep: Future Directions

A major challenge to the field is reconciling SHY with findings that show that sleep also increases synaptic strength (Aton et al. 2009, 2014; Chauvette et al. 2012; Dumoulin et al. 2013; Seibt et al. 2012). One possibility is that "replay-reactivation" occurs against a background of global downscaling. For example, sleep during the early part of the rest phase may express high levels of replay (leading to synaptic potentiation) that then declines. Coincident with replay is a slower, non-Hebbian scaling event which progressively asserts greater influence as replay fades. As this downscaling affects all synapses in proportion to their strength, the relative differences in strength are preserved. This is consistent with the time course of replay during sleep and properties of non-Hebbian synaptic scaling as originally described by Turrigiano. This is also predicted by the "Boom and Bust" model shown in Fig. 3 and other theories that posit dual effects of sleep on synaptic strength (Genzel et al. 2014; Giuditta 1995; Ribeiro 2011). It also leads to testable predictions. For example, if early sleep is essential for synaptic strengthening, then sleep deprivation, or manipulations of signaling pathways during early sleep, should predominantly interfere with synaptic potentiation. This

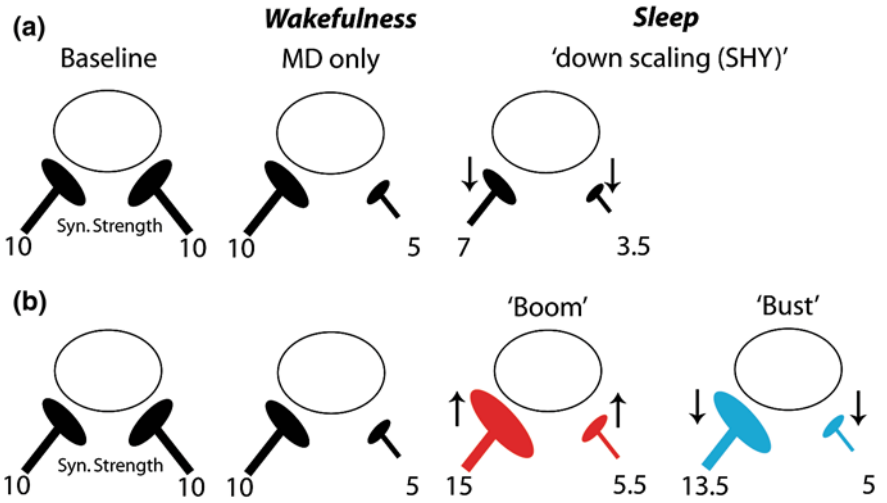

Fig. 3 A "Boom and Bust" model of sleep-dependent plasticity explains the effects of sleep on ocular dominance plasticity. The initial effects of Monocular Deprivation (MD) in the cat are a weakening of responses to the deprived eye during wakefulness. After sleep, there is no further weakening in deprived eye circuits and instead responses to the nondeprived eye become stronger. **a** According to the Synaptic Homeostasis Hypothesis (SHY), sleep globally downscales synaptic strength in a manner proportionate to the strength at each synapse. This produces no net potentiation in the nondeprived circuits and increases depression in the deprived eye pathways. **b** According to the Boom and Bust model, sleep immediately after experience leads to synaptic potentiation ("Boom"). This is likely Hebbian, but may involve heterosynaptic changes due to synaptic tagging and capture of plasticity-related proteins in neighboring synapses (Redondo et al. 2010). As sleep progresses, global downscaling ensues, which reduces synaptic strength proportionately at each synapse ("Bust"). The net result is potentiation in the nondeprived eye pathways, and no further modifications in the deprived eye circuits, which fits empirical data. For illustration purposes, arbitrary units of synaptic strength are shown

is obviously an oversimplification of what might actually occur in the sleeping brain, as changes in one sleep state might set in motion changes in another (Benington and Heller 1994; Giuditta 1995). However, it is generally supported by several results in the developing cat. Sleep deprivation in the first 2 h of post-MD sleep reduces kinase activation and protein synthesis. NMDAR blockage during the first few hours of post-MD sleep inhibits sleep-dependent plasticity, but this inhibition does not occur when blockage occurs later in the sleep period (Aton et al. 2009). Similar results are obtained when all cortical activity is silenced during post-MD sleep (Jha et al. 2005).

However, any attempt to integrate theories like SHY with findings in the developing and adult brain requires further identification of the cellular mechanisms governing SHY. It is essential that circadian factors be eliminated as variables in measurements of plasticity. This is a formidable, unaddressed problem in studies that use laboratory animals with strong circadian rhythms in hormone release and brain temperature. A very simple means of controlling for circadian

cycles in glucocorticoid release is to combine adrenalectomy with hormone pellets. This results in a flat, continuous release of stress hormones and allows for the isolation of biological changes due to sleep and wake, versus those driven by circadian rhythms in HPA activity. As recently shown by Mongrain et al., this technique has already been used to identify state-driven molecular changes in the brain (Mongrain et al. 2010). Therefore, a similar approach could determine which of the reported changes in synapses observed after sleep or wake are truly state-dependent, or instead driven by the HPA. Controlling for circadian changes in brain temperature in mammals is technically more challenging, but this is feasible in ectothermic insects such as the fruit fly. It would be interesting to track core temperature in these animals across the normal sleep-wake cycle and determine if natural fluctuations under typical laboratory conditions are within the range known to influence synaptic morphology in this species.

It is also critical to conduct direct tests of hypothesized relationships between synaptic plasticity and sleep function. If sleep need arises from synaptic potentiation, then mutations in fruit flies or mice that reduce synaptic potentiation should also reduce sleep need. There are a number of mutant mouse lines with profound reductions in LTP, but these mice have not been examined with respect to sleep (Frank 2012). These mutations can also now be experimentally induced, particularly in fruit flies, with increasingly fine temporal precision. These techniques thus do not suffer from limitations of constitutive mutations (i.e., developmental compensation in embryonic "knock-outs") and can provide potentially powerful and direct tests of current theory. There is now no reasonable objection to pursuing these direct tests of SHY (or similar theories).

A second set of important experiments to conduct are those aimed at ascertaining the function of synaptic changes observed after sleep. More specifically, there is currently no empirical evidence that downscaling of synapses reported after sleep in rodents has any function (Tononi and Cirelli 2014). In addition, many findings cited in support of SHY are derived from nonphysiological manipulations (i.e., forms of stimulation not naturally experienced by the intact brain, or measurement conditions that do not reproduce the conditions of the intact brain (Albensi et al. 2007; Holscher 1999)). These include 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), and transcranial electromagnetic fields (Huber 2007). None of these conditions occur naturally in animals.

In contrast, synaptic changes noted after MD, OSRP, and sleep are part of an endogenous response to changes in sensory experience in vivo. There is also increasing evidence that hippocampal replay of waking experience in sleep leads to adaptive changes in the brain. Therefore, *direct* tests of how "down-scaled" synapses in sleep lead to adaptive changes (behaviorally or otherwise) are now needed. One promising approach along these lines is recent work in *Drosophila* (Donlea et al. 2011). It has been shown in fruit flies that certain forms of experience can saturate synapse number which prevents certain forms of learning.

Learning can be rescued after a period of sleep, which also reduces synapses. It will therefore be important to determine if these findings generalize to other circuits in *Drosophila*, and to other species.

References

Aghajanian GK, Bloom FE (1967) The formation of synaptic junctions in developing rat brain: a quantitative electron microscopic study. Brain Res 6:716–727

Albensi BC, Oliver DR, Toupin J, Odero G (2007) Electrical stimulation protocols for hippocampal synaptic plasticity and neuronal hyper-excitability: are they effective or relevant? Exp Neurol 204:1–13

Alfoldi P, Tobler I, Borbely AA (1990) Sleep regulation in rats during early development. Am J Physiol 258:R634–R644

Arrigoni E, Lu J, Vetrivelan R, Saper CB (2009) Long-term synaptic plasticity is impaired in rats with lesions of the ventrolateral preoptic nucleus. Eur J Neurosci 30:2112–2120

Aton SJ, Broussard C, Dumoulin M, Seibt J, Watson A, Coleman T, Frank MG (2013) Visual experience and subsequent sleep induce sequential plastic changes in putative inhibitory and excitatory cortical neurons. Proc Natl Acad Sci USA 110:3101–3106

Aton SJ, Seibt J, Dumoulin M, Jha SK, Steinmetz N, Coleman T, Naidoo N, Frank MG (2009) Mechanisms of sleep-dependent consolidation of cortical plasticity. Neuron 61:454–466

Aton SJ, Suresh A, Broussard C, Frank MG (2014) Sleep promotes cortical response potentiation following visual experience. Sleep (in press)

Battaglia FP, Sutherland GR, McNaughton BL (2004) Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. Learn Mem 11:697–704

Bear MF, Malenka RC (1994) Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol 4:389–399

Bendor D, Wilson MA (2012) Biasing the content of hippocampal replay during sleep. Nat Neurosci 15:1439–1444

Benington JH, Frank MG (2003) Cellular and molecular connections between sleep and synaptic plasticity. Prog Neurobiol 69:77–101

Benington JH, Heller HC (1994) Does the function of REM sleep concern non-REM sleep or waking? Prog Neurobiol 44:433–449

Bittar P, Muller D (1993) Time-dependent reversal of long-term potentiation by brief cooling shocks in rat hippocampal slices. Brain Res 620:181–188

Buisseret P, Imbert M (1976) Visual cortical cells: their developmental properties in normal and dark reared kittens. J Physiol 255:511–525

Buzsaki G (1996) The hippocampo-neocortical dialogue. Cereb Cortex 6:81–92

Campbell IG, Guinan MJ, Horowitz JM (2002) Sleep deprivation impairs long-term potentiation in the rat hippocampal slices. J Neurophysiol 88:1073–1076

Chauvette S, Seigneur J, Timofeev I (2012) Sleep oscillations in the thalamocortical system induce long-term neuronal plasticity. Neuron 75:1105–1113

Chen C, Hardy M, Zhang J, LaHoste GJ, Bazan NG (2006) Altered NMDA receptor trafficking contributes to sleep deprivation-induced hippocampal synaptic and cognitive impairments. Biochem Biophys Res Commun 340:435–440

Conboy L, Sandi C (2009) Stress at learning facilitates memory formation by regulating AMPA receptor trafficking through a glucocorticoid action. Neuropsychopharmacology 35:674–685

Cooke SF, Bear MF (2010) Visual experience induces long-term potentiation in the primary visual cortex. J Neurosci 30:16304–16313

Crair MC, Ruthazer ES, Gillespie DC, Stryker MP (1997) Relationship between the ocular dominance and orientation maps in visual cortex of monocularly deprived cats. Neuron 19:307–318

Crick F, Mitchison G (1983) The function of dream sleep. Nature 304:111–114

Crick F, Mitchison G (1995) REM sleep and neural nets. Behav Brain Res 69:147–155

Dadvand L, Stryker MP, Frank MG (2006) Sleep does not enhance the recovery of deprived eye responses in developing visual cortex. Neuroscience 143:815–826

Daftary SS, Panksepp J, Dong Y, Saal DB (2009) Stress-induced, glucocorticoid-dependent strengthening of glutamatergic synaptic transmission in midbrain dopamine neurons. Neurosci Lett 452:273–276

Dave AS, Margoliash D (2000) Song replay during sleep and computational rules of sensorimotor vocal learning. Science 290:812–816

Davis CJ, Harding JW, Wright JW (2003) REM sleep deprivation-induced deficits in the latency-to-peak induction and maintenance of long-term potentiation within the CA1 region of the hippocampus. Brain Res 973:293–297

Davis CJ, Meighan PC, Taishi P, Krueger JM, Harding JW, Wright JW (2006) REM sleep deprivation attenuates actin-binding protein cortactin: a link between sleep and hippocampal plasticity. Neurosci Lett 400:191–196

Daw NW, Sato H, Fox K, Carmichael T, Gingerich R (1991) Cortisol reduces plasticity in the kitten visual cortex. J Neurobiol 22:158–168

de Villers-Sidani E, Merzenich MM (2011) Chapter 8—Lifelong plasticity in the rat auditory cortex: basic mechanisms and role of sensory experience. In: Chapman CE, Kalaska JF, Green AM, Franco L (eds) Progress in brain research, Elsevier, pp 119–131

Deuker L, Olligs J, Fell J, Kranz TA, Mormann F, Montag C, Reuter M, Elger CE, Axmacher N (2013) Memory consolidation by replay of stimulus-specific neural activity. J Neurosci 33:19373–19383

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126

Donlea JM, Thimgan MS, Suzuki Y, Gottschalk L, Shaw PJ (2011) Inducing sleep by remote control facilitates memory consolidation in Drosophila. Science 332:1571–1576

Dumoulin MC, Aton S, Watson A, Coleman T, Frank MG (2013) ERK activity during sleep is necessary for the consolidation of cortical plasticity. Cerebral cortex (in press)

Ego-Stengel V, Wilson MA (2010) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20:1–10

Espinosa JS, Stryker MP (2012) Development and plasticity of the primary visual cortex. Neuron 75:230–249

Fagiolini M, Pizzorusso T, Berardi N, Domenici L, Maffei L (1994) Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. Vision Res 34:709–720

Faraguna U, Nelson A, Vyazovskiy VV, Cirelli C, Tononi G (2010) Unilateral cortical spreading depression affects sleep need and induces molecular and electrophysiological signs of synaptic potentiation in vivo. Cereb Cortex 20:2939–2947

Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C (2008) A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. J Neurosci 28:4088–4095

Florian CD, Vecsey CG, Halassa MM, Haydon PG, Abel T (2011) Astrocyte-derived adenosine and A1 receptor activity contribute to sleep loss-induced deficits in hippocampal synaptic plasticity and memory in mice. J Neurosci 31:6956–6962

Foeller E, Feldman DE (2004) Synaptic basis for developmental plasticity in somatosensory cortex. Curr Opin Neurobiol 14:89–95

Foster DJ, Wilson MA (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature 440:680–683

Frank MG (2007) Hippocampal dreams, cortical wishes: a closer look at neuronal replay and the hippocampal-neocortical dialogue during sleep. Cell Sci Rev 3:161–171

Frank MG (2011) Sleep and developmental brain plasticity: not just for kids. Prog Brain Res 193:221–232

Frank MG (2012) Erasing synapses in sleep: is it time to be SHY? Neural Plasticity 2012:264–378
Frank MG (2013) Why I'm not SHY: a reply to Tononi and Cirelli. Neural plasticity 2013:394–946
Frank MG, Benington J (2006) The role of sleep in brain plasticity: dream or reality? Neurosci 12:477–488
Frank MG, Heller HC (1997) Development of REM and slow wave sleep in the rat. Am J Physiol 272:R1792–R1799
Frank MG, Issa NP, Stryker MP (2001) Sleep enhances plasticity in the developing visual cortex. Neuron 30:275–287
Frank MG, Jha SK, Coleman T (2006) Blockade of postsynaptic activity in sleep inhibits developmental plasticity in visual cortex. NeuroReport 17:1459–1463
Frank MG, Morrissette R, Heller HC (1998) Effects of sleep deprivation in neonatal rats. Am J Physiol 275:R148–R157
Franken P, Dijk DJ, Tobler I, Borbely AA (1991) Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. Am J Physiol 261:R198–R208
Franken P, Tobler I, Borbely AA (1993) Effects of 12-h sleep deprivation and of 12-h cold exposure on sleep regulation and cortical temperature in the rat. Physiolo Behav 54:885–894
Genzel L, Kroes MCW, Dresler M, Battaglia FP (2014) Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? Trends Neurosci 37:10–19
Girardeau G, Benchenane K, Wiener SI, Buzsaki G, Zugaro MB (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12:1222–1223
Girardeau G, Zugaro M (2011) Hippocampal ripples and memory consolidation. Curr Opin Neurobiol 252:452–459
Giuditta A (1995) The sequential hypothesis of the function of sleep. Behav Brain Res 69:157–166
Glotzbach SF, Heller HC (2000) Temperature regulation. In: Roth C, Kryger M, Dement WC (eds) Principles and practice of sleep medicine. Saunders, Philadelphia, pp 289–304
Graves L, Pack A, Abel T (2001) Sleep and memory: a molecular perspective. Trends Neurosci 24:237–243
Groc L, Choquet D, Chaouloff F (2008) The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. Nat Neurosci 11:868–870
Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation. J Physiol (Lond) 575:807–819
Hanlon EC, Vyazovskiy VV, Faraguna U, Tononi G, Cirelli C (2011) Synaptic potentiation and sleep need: clues from molecular and electrophysiological studies. Curr Top Med Chem 11:2472–2482
Hasselmo ME (1999) Neuromodulation: acetylcholine and memory consolidation. Trends Cogn Sci 3:351–359
Heinrich B (1974) Thermoregulation in endothermic insects. Science 185:747–756
Hengen KB, Lambo ME, Van Hooser SD, Katz DB, Turrigiano GG (2013) Firing rate homeostasis in visual cortex of freely behaving rodents. Neuron 80:335–342
Hennevin E, Huetz C, Edeline J-M (2007) Neural representations during sleep: from sensory processing to memory traces. Neurobiol Learn Mem 87:416–440
Hoffman KL, McNaughton BL (2002) Coordinated reactivation of distributed memory traces in primate cortex. Science 297:2070–2073
Holscher C (1999) Synaptic plasticity and learning and memory: LTP and beyond. J Neurosci Res 58:62–75
Hubel DH, Wiesel TN (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J Physiol 206:419–436
Huber R (2007) TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. PLoS ONE 2:e276

Ishikawa A, Kanayama Y, Matsumura H, Tsuchimochi H, Ishida Y, Nakamura S (2006) Selective rapid eye movement sleep deprivation impairs the maintenance of long-term potentiation in the rat hippocampus. Eur J Neurosci 24:243–248

Jha SK, Jones BE, Coleman T, Steinmetz N, Law C, Griffin G, Hawk J, Frank MG (2005) Sleep-dependent plasticity requires cortical activity. J Neurosci 25:9266–9274

Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10:100–106

Joels M, Krugers H, Karst H (2008) Stress-induced changes in hippocampal function. Prog Brain Res 167:3–15

Jouvet-Mounier D, Astic L, Lacote D (1970) Ontogenesis of the states of sleep in rat, cat and guinea pig during the first postnatal month. Dev Psychobiol 2:216–239

Karst H, Joels M (2005) Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. J Neurophysiol 94:3479–3486

Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsaki G (2004) Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature 432:758–761

Kim E, Mahmoud GS, Grover LM (2005) REM sleep deprivation inhibits LTP in vivo in area CA1 of rat hippocampus. Neurosci Lett 388:163–167

Kirkwood A, Lee HK, Bear MF (1995) Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex. Nature 375:328–331

Komatsuzaki Y, Hatanaka Y, Murakami G, Mukai H, Hojo Y, Saito M, Kimoto T, Kawato S (2012) Corticosterone induces rapid spinogenesis via synaptic glucocorticoid receptors and kinase networks in hippocampus. PLoS ONE 7:e34124

Kopp C, Longordo F, Nicholson JR, Luthi A (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. J Neurosci 26:12456–12465

Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience and EEG dynamics. J Neurosci 19:4090–4101

Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36:1183–1194

Liston C, Cichon JM, Jeanneteau F, Jia Z, Chao MV, Gan W-B (2013) Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. Nat Neurosci 16:698–705

Liu W, Yuen EY, Yan Z (2010) The stress hormone corticosterone increases synaptic amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors via serum- and glucocorticoid-inducible kinase (SGK) regulation of the GDI-Rab4 complex. J Biol Chem 285: 6101–6108

Longordo F, Kopp C, Mishina M, Lujan R, Luthi A (2009) NR2A at CA1 synapses is obligatory for the susceptibility of hippocampal plasticity to sleep loss. J Neurosci 29:9026–9041

Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29:145–156

Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44:5–21

Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, Del Fiore G, Degueldre C, Meulemans T, Luxen A, Franck G, Van Der Linden M, Smith C, Cleeremans A (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3:831–836

Maret S, Faraguna U, Nelson AB, Cirelli C, Tononi G (2011) Sleep and waking modulate spine turnover in the adolescent mouse cortex. Nat Neurosci (advance online publication)

Markram H, Gerstner W, Sjostrom PJ (2011) A history of spike-timing-dependent plasticity. Front Synaptic Neurosci 3:1–24

Marks CA, Wayner MJ (2005) Effects of sleep disruption on rat dentate granule cell LTP in vivo. Brain Res Bull 66:114–119

McDermott CM, Hardy MN, Bazan NG, Magee JC (2005) Sleep-deprivation induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus J Physiol (Lond). doi: 10.1113/jphysiol.2005.093781

McDermott CM, Hardy MN, Bazan NG, Magee JC (2006) Sleep deprivation-induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. J Physiol (Lond) 570:553–565

McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003) Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 23:9687–9695

Mioche L, Singer W (1989) Chronic recordings from single sites of kitten striate cortex during experience-dependent modifications of receptive-field properties. J Neurophysiol 62:185–197

Miyamoto H, Katagiri H, Hensch T (2003) Experience-dependent slow-wave sleep development. Nat Neurosci 6:553–554

Mongrain V, Hernandez SA, Pradervand S, Dorsaz S, Curie T, Hagiwara G, Gip P, Heller HC, Franken P (2010) Separating the contribution of glucocorticoids and wakefulness to the molecular and electrophysiological correlates of sleep homeostasis. Sleep 33:1147–1157

Moser E, Mathiesen I, Andersen P (1993) Association between brain temperature and dentate field potentials in exploring and swimming rats. Science 259:1324–1326

O'Neill J, Senior T, Csicsvari J (2006) Place-selective firing of CA1 pyramidal cells during sharp wave/ripple network patterns in exploratory behavior. Neuron 49:143–155

Olijslagers JE, de Kloet ER, Elgersma Y, van Woerden GM, Joels M, Karst H (2008) Rapid changes in hippocampal CA1 pyramidal cell function via pre- as well as postsynaptic membrane mineralocorticoid receptors. Eur J Neurosci 27:2542–2550

Olson C, Freeman RD (1975) Progressive changes in kitten striate cortex during monocular deprivation. J Neurophysiol 38:26–32

Olson C, Freeman RD (1980) Profile of the sensitive period for monocular deprivation in kittens. Exp Brain Res 39:17–21

Pavlides C, Winson J (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep. J Neurosci 9:2907–2918

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44:535–545

Peng IF, Berke BA, Zhu Y, Lee W-H, Chen W, Wu C-F (2007) Temperature-dependent developmental plasticity of drosophila neurons: cell-autonomous roles of membrane excitability, Ca2+ influx, and cAMP signaling. J Neurosci 27:12611–12622

Pennartz CMA, Lee E, Verheul J, Lipa P, Barnes CA, McNaughton BL (2004) The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. J Neurosci 24:6446–6456

Peyrache A, Khamassi M, Benchenane K, Wiener SI, Battaglia FP (2009) Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nat Neurosci 12:919–926

Poe GR, Nitz DA, McNaughton BL, Barnes CA (2000) Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. Brain Res 855:176–180

Pozo K, Goda Y (2010) Unraveling mechanisms of homeostatic synaptic plasticity. Neuron 66:337–351

Qin YL, McNaughton BL, Skaggs WE, Barnes CA (1997) Memory reprocessing in cortiocortical and hippocampalcortical neuronal ensembles. Philos Trans R Soc Lond B Biol Sci 352: 1525–1533

Ravassard P, Pachoud B, Comte J, Gay N, Touret M, Luppi P, Salin PA (2006) Paradoxical sleep amount modulates neuronal plasticity in adult rat hippocampus. J Sleep Res 15:191

Ravassard P, Pachoud B, Comte JC, Mejia-Perez C, Scote-Blachon C, Gay N, Claustrat B, Touret M, Luppi PH, Salin PA (2009) Paradoxical (REM) sleep deprivation causes a large and rapidly reversible decrease in long-term potentiation, synaptic transmission, glutamate receptor protein levels, and ERK/MAPK activation in the dorsal hippocampus. Sleep 32:227–240

Redondo RL, Okuno H, Spooner PA, Frenguelli BG, Bito H, Morris RGM (2010) Synaptic tagging and capture: differential role of distinct calcium/calmodulin kinases in protein synthesis-dependent long-term potentiation. J Neurosci 30:4981–4989

Ribeiro S (2004) Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas. PLoS Biol 2:e24
Ribeiro S (2007) Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. Front Neurosci 1:43–55
Ribeiro S (2011) Sleep and plasticity. Pflugers Archiv Eur J Physiol 1–10
Roelandse M, Matus A (2004) Hypothermia-associated loss of dendritic spines. J Neurosci 24:7843–7847
Roffwarg HP, Muzio JN, Dement WC (1966) Ontogenetic development of the human sleep-dream cycle. Science 152:604–619
Romcy-Pereira R, Pavlides C (2004) Distinct modulatory effects of sleep on the maintenance of hippocampal and medial prefrontal cortex LTP. Eur J Neurosci 20:3453–3462
Sato M, Stryker MP (2008) Distinctive features of adult ocular dominance plasticity. J Neurosci 28:10278–10286
Satoh E, Shimeki S (2010) Acute restraint stress enhances calcium mobilization and glutamate exocytosis in cerebrocortical synaptosomes from mice. Neurochem Res 35:693–701
Sawtell NB, Frenkel MY, Philpot BD, Nakazawa K, Tonegawa S, Bear MF (2003) NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. Neuron 38:977–985
Schönauer M, Geisler T, Gais S (2013) Strengthening procedural memories by reactivation in sleep. J Cogn Neurosci 26:143–153
Schwindel DC, McNaughton B (2011) Hippocampal-cortical interactions and the dynamics of memory trace activation. Prog Brain Res 193:163–177
Seibt J, Dumoulin M, Aton SJ, Naidoo J, Watson A, Coleman T, Frank MG (2012) Protein synthesis during sleep consolidates cortical plasticity in vivo. Curr Biol 22:676–682
Seibt J, Frank MG (2012) Translation regulation in sleep: making experience last. Communicative and integrative biology (in Press)
Sengpiel F, Godecke I, Stawinski P, Hubener M, Lowel S, Bonhoffer T (1998) Intrinsic and environmental factors in the development of functional maps in cat visual cortex. Neuropharmacology 37:607–621
Shaffery JP, Lopez J, Bissette G, Roffwarg HP (2005) Rapid eye movement sleep deprivation revives a form of developmentally regulated synaptic plasticity in the visual cortex of post-critical period rats. Neurosci Lett 391:131–135
Shaffery JP, Lopez J, Roffwarg HP (2012) Brain-derived neurotrophic factor (BDNF) reverses the effects of rapid eye movement sleep deprivation (REMSD) on developmentally regulated, long-term potentiation (LTP) in visual cortex slices. Neurosci Lett 513:84–88
Shaffery JP, Roffwarg HP (2003) Rapid eye-movement sleep deprivation does not 'rescue' developmentally regulated long-term potentiation in visual cortex of mature rats. Neurosci Lett 342:196–200
Shaffery JP, Sinton CM, Bissette G, Roffwarg HP, Marks GA (2002) Rapid eye movement sleep deprivation modifies expression of long-term potentiation in visual cortex of immature rats. Neuroscience 110:431–443
Siapas AG, Wilson MA (1998) Coordinated interations between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21:1123–1128
Simkus CRL, Stricker C (2002) Properties of mEPSCs recorded in layer II neurones of rat barrel cortex. J Physiol 545:509–520
Singer W (1979) Neuronal mechanisms in experience dependent modification of visual cortex function. In: Cuenod M, Kreutzberg GW, Bloom FE (eds) Development and chemical sensitivity of neurons. Elsevier/North-Holland Biomedical Press, Amsterdam, pp 457–477
Sirota A, Csicsvari J, Buhl D, Buzsaki G (2003) Communication between neocortex and hippocampus during sleep in rodents. PNAS 100:2065–2069
Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271:1870–1873
Steriade M, Timofeev I (2003) Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 37:563–576

Stevenson RD (1985) Body size and limits to the daily range of body temperature in terrestrial ectotherms. Am Nat 125:102–117
Sur M, Leamey CA (2001) Development and plasticity of cortical areas and networks. Nat Rev Neurosci 2:251–262
Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, Brown RE, Strecker RE (2006) Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. Eur J Neurosci 23:2739–2748
Tatsuno M, Lipa P, McNaughton BL (2006) Methodological considerations on the use of template matching to study long-lasting memory trace replay. J Neurosci 26:10727–10742
Thurber A, Jha SK, Coleman T, Frank MG (2008) A preliminary study of sleep ontogenesis in the ferret (Mustela putorius furo). Behav Brain Res 189:41–51
Tiriac A, Uitermarkt BD, Fanning AS, Sokoloff G, Blumberg MS (2012) Rapid whisker movements in sleeping newborn rats. Curr Biol 22:2075–2080
Tononi G (2009) Slow wave homeostasis and synaptic plasticity. J Clin Sleep Med 5:S16–S19
Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
Tononi G, Cirelli C (2012) Time to be SHY? some comments on sleep and synaptic homeostasis. Neural plasticity (in press)
Tononi G, Cirelli C (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81:12–34
Tropea D, Van Wart A, Sur M (2009) Molecular mechanisms of experience-dependent plasticity in visual cortex. Philos Trans R Soc B Biol Sci 364:341–355
Tsanov M, Manahan-Vaughan D (2007) The adult visual cortex expresses dynamic synaptic plasticity that is driven by the light/dark cycle. J Neurosci 27:8414–8421
Tse YC, Bagot RC, Wong TP (2012) Dynamic regulation of NMDAR function in the adult brain by the stress hormone corticosterone. Front Cell Neurosci 6:9
Turrigiano G (2007) Homeostatic signaling: the positive side of negative feedback. In: Cull-Candy S, Klein R (eds) Curr Opin Neurobiol Signal mech 17:318–324
Turrigiano GG (1999) Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. Trends Neurosci 22:221–227
Turrigiano GG (2008) The self-tuning neuron: synaptic scaling of excitatory synapses. Cell 135:422–435
Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB (1998) Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature 391:892–896
Turrigiano GG, Nelson SB (2000) Hebb and homeostasis in neuronal plasticity. Curr Opin Neurobiol 10:358–364
Van Cauter E (2005) Endocrine physiology. In: Kryger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine. Elsevier, Philadelphia, pp 266–282
Vanin S, Bhutani S, Montelli S, Menegazzi P, Green EW, Pegoraro M, Sandrelli F, Costa R, Kyriacou CP (2012) Unexpected features of Drosophila circadian behavioural rhythms under natural conditions. Nature 484:371–375
Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li X-Y, Descalzi G, Kim SS, Chen T, Shang Y-Z, Zhuo M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. Nature 461:1122–1125
Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11:200–208
Wiesel TN, Hubel DH (1963) Single cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 28:1029–1040
Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–682

Yang G, Gan W.-B (2011) Sleep contributes to dendritic spine formation and elimination in the developing mouse somatosensory cortex. Dev Neurobiol 72:1391–1398

Yuen EY, Liu W, Karatsoreos IN, Ren Y, Feng J, McEwen BS, Yan Z (2011) Mechanisms for acute stress-induced enhancement of glutamatergic transmission and working memory. Mol Psychiatry 16:156–170

Zhong Y, Wu C-F (2004) Neuronal activity and adenylyl cyclase in environment-dependent plasticity of axonal outgrowth in Drosophila. J Neurosci 24:1439–1445

Sleep and Adult Neurogenesis: Implications for Cognition and Mood

Anka D. Mueller, Peter Meerlo, Dennis McGinty and Ralph E. Mistlberger

Abstract The hippocampal dentate gyrus plays a critical role in learning and memory throughout life, in part by the integration of adult-born neurons into existing circuits. Neurogenesis in the adult hippocampus is regulated by numerous environmental, physiological, and behavioral factors known to affect learning and memory. Sleep is also important for learning and memory. Here we critically examine evidence from correlation, deprivation, and stimulation studies that sleep may be among those factors that regulate hippocampal neurogenesis. There is mixed evidence for correlations between sleep variables and rates of hippocampal cell proliferation across the day, the year, and the lifespan. There is modest evidence that periods of increased sleep are associated with increased cell proliferation or survival. There is strong evidence that disruptions of sleep exceeding 24 h, by total deprivation, selective REM sleep deprivation, and chronic restriction or fragmentation, significantly inhibit cell proliferation and in some cases neurogenesis. The mechanisms by which sleep disruption inhibits neurogenesis are not fully understood. Although sleep disruption procedures are typically at least mildly stressful, elevated adrenal corticosterone secretion is not necessary for this effect. However, procedures that prevent both elevated corticosterone and interleukin 1β signaling have been found to block the effect of sleep deprivation on cell proliferation. This result suggests that sleep loss impairs hippocampal neurogenesis by the presence of wake-dependent factors, rather than by the absence of sleep-specific processes. This would weigh against a hypothesis that regulation of neurogenesis is a function of sleep.

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Nonetheless, impaired neurogenesis may underlie some of the memory and mood effects associated with acute and chronic sleep disruptions.

Keywords Neurogenesis · Hippocampus · Sleep deprivation · Corticosterone · BrdU

Contents

1 Sleep and Adult Hippocampal Neurogenesis: Conceptual Issues

It is now well established that new neurons are generated in the adult mammalian brain from precursor stem-like cells that divide, differentiate, migrate, and mature

into typical neurons, but, as in the embryo, may also fail to survive. This process, called adult neurogenesis, persists at significant levels throughout life in both the subgranular zone of the hippocampal dentate gyrus and the subventricular zone along the lateral ventricular walls. A fraction of these new neurons are functionally integrated into the preexisting neuronal network (Lledo et al. 2006; Ming and Song 2011). The objective of this chapter is to evaluate evidence for a relationship between sleep and regulation of hippocampal neurogenesis in adult mammals. The rationale for exploring a functional link between sleep and neurogenesis is based on a number of associations among sleep, hippocampal functions, and factors known to regulate neurogenesis.

1. Sleep disruption affects hippocampal plasticity and learning and memory functions. Adult-born neurons represent a form of hippocampal plasticity and are thought to participate in these functions.
2. Chronic stress disrupts sleep, impairs hippocampal function, and inhibits hippocampal neurogenesis. Sleep disruption could mediate or potentiate stress effects on hippocampal function and neurogenesis.
3. Sleep disruption per se can evoke stress responses, which could be sufficient to inhibit hippocampal neurogenesis.
4. Depression is commonly associated with sleep disruption and has also been associated with a reduced hippocampal volume, which could result, in part, from chronic suppression of neurogenesis.
5. Aging is commonly associated with reduced sleep, more complaints of insomnia, and a decline of cognitive functions, including those attributed to the hippocampus. Aging is also associated with reduced hippocampal neurogenesis.
6. Many endogenous factors that regulate adult neurogenesis, including neurotransmitters, hormones, and cytokines vary with the sleep-wake cycle. One factor, growth hormone, exhibits sleep-facilitated release in some species. Sensitivity to some factors is altered by sleep deprivation (e.g., by changes in receptor number or affinity).

The following sections provide an overview of adult neurogenesis, highlighting its discovery, the location of neurogenic niches in the brain, the sequence of stages in neurogenesis, immunocytochemical procedures for identifying these stages, the regulation of these stages by endogenous and exogenous stimuli, and the proposed functions of new neurons, with a special focus on hippocampal neurogenesis. Evidence for the role of sleep in adult neurogenesis is then reviewed, from studies employing correlation, deprivation, or stimulation methods.

2 Major Milestones in the Discovery of Adult Neurogenesis

Historically, a central dogma in developmental neurobiology was that neurogenesis in mammals is complete early in life and is absent in the brains of adults.

The provocative new idea of adult neurogenesis was introduced in the 1960s by Altman, who found evidence for new cells in the dentate gyrus of the hippocampus (Altman and Das 1965) and the olfactory bulb (Altman 1969) of adult rats, using [H^3]-thymidine autoradiography. Kaplan and Hinds (1977) later provided ultrastructural evidence for synaptic innervation of adult-born neurons, but these findings did not fully succeed in overturning the rule of "no-new-neurons." The notion that adult-born neurons could be functionally significant gained acceptance with work on song learning in songbirds (Paton and Nottebohm 1984). Neurogenesis research involving adult mammals was revived in the 1990s, when stem cells were isolated from the brain of adult rodents and induced to proliferate and express neuronal phenotypes in vitro and in vivo (Reynolds and Weiss 1992; Cameron et al. 1993). The current era of adult neurogenesis research gained momentum with the introduction of immunohistochemical methods for labeling newly divided cells using antibodies to a synthetic thymidine analog, 5′-bromo-2-deoxyuridine (BrdU) that is incorporated into DNA during the S-phase of the cell cycle in mitotically active cells (Gratzner 1982). The availability of immunomarkers to distinguish new neurons from glial cells provided convincing evidence for adult neurogenesis in the dentate gyrus across a range of mammalian species, including rats (laboratory and wild caught), mice, monkeys (Gould et al. 1999b), and humans (Eriksson et al. 1998; Manganas et al. 2007). Integration of newly generated cells into the hippocampal network has now been established (van Praag et al. 2002), and the focus of current efforts is to understand the regulation and functional role of new neurons in these circuits. Another research question is whether new neurons are produced in and make functional contributions to other brain regions. A second confirmed neurogenic niche is the subventricular zone along the wall of the lateral cerebral ventricles, which produces neurons that migrate to the olfactory bulb (Lois and Alvarez-Buylla 1994). The presence of adult-born neurons in other brain regions, including the neocortex, striatum, and hypothalamus, is less well established or controversial (Bonfanti and Peretto 2011; Lee and Blackshaw 2012). The relationship between sleep and adult neurogenesis has so far been examined primarily in the hippocampus, and to a lesser extent the subventricular zone, and consequently other regions will not be discussed further.

3 Stages, Cell Types, and Detection Methods

Adult neurogenesis includes cell proliferation, differentiation, maturation, migration, survival, and functional integration of new neurons into brain circuits. Stem/progenitor cells that can divide and differentiate into neurons, astrocytes, or oligodendrocytes are located in the subgranular zone, a thin layer between the granular cell layer and the hilus of the hippocampal formation. Although the lineage relationship between the different cell types is still under investigation, it is believed that neural stem/progenitor cells progress to intermediate progenitor cells by asymmetric and potentially symmetric cell division (Kempermann 2011a).

Intermediate progenitors, also called transient amplifying cells, proliferate in this neurogenic niche and produce clusters of new cells (Palmer et al. 2000). These new cells can then develop into neuroblasts, which migrate from the neurogenic niche to the inner granule cell layer of the dentate gyrus, where they mature into granule cells within 4–8 weeks (Cameron et al. 1993; Ming and Song 2011). For details see Fig. 1.

Newborn neurons undergo morphological and physiological maturation by extending axons into the hippocampal CA3 region and dendrites into the molecular layer of the dentate gyrus (Stanfield and Trice 1988; Gu et al. 2012). Inputs from the entorhinal cortex stimulate formation of spines and functional synapses (Markakis and Gage 1999; Zhao et al. 2006). Immature neurons are at first tonically depolarized by gamma-aminobutyric acid (GABA) released from interneurons. Depolarizing GABAergic input was found to increase proliferation and differentiation in the neuronal precursors (Tozuka et al. 2005; Ge et al. 2007a). A final step in neurogenesis is reception of synaptic glutamate input via AMPA and NMDA receptors, which mediate depolarization and promote survival of newborn neurons (Tashiro et al. 2006). Young neurons are hyperexcitable, which is thought to enhance their participation in synaptic plasticity. A portion of the new neurons will be integrated into the hippocampal network over a time span of 2 months, during which axosomatic, axodentritic, and axospinous synaptic contacts are established (van Praag et al. 2002; Toni et al. 2007). Survival is experience and input dependent and over 50 % of new cells die by apoptosis, many within the first few days after exiting the cell cycle (Dayer et al. 2003; Tashiro et al. 2007; Sierra et al. 2010).

Most studies have used immunocytochemical detection of BrdU as a cell proliferation marker (Taupin 2007). After BrdU injection, brains are collected for processing at a time determined by the research question. To identify newly proliferating cells, brains are typically harvested 2 h after BrdU injection (approximate duration of BrdU bioavailability), which captures cells in the S-phase ($\sim$7–9 h in rats) before entering mitotic cell division (Figs. 2a, 5a). If cell survival is of interest, animals are kept alive for days to weeks after BrdU injection (Figs. 2b, 5b). The population of cells labeled by a single injection of BrdU doubles over about 2 days, and may expand for up to 4 days (Dayer et al. 2003). Therefore, to measure the effects of a procedure (e.g., sleep deprivation) on survival, independent of proliferation, BrdU must be administered 4 or more days prior to the procedure. Endogenous mitotic cell cycle stage-specific proteins can also be immunolabeled to identify proliferating cells. For example, Ki67 (Fig. 2c), a nuclear protein, is expressed during all phases of the cell cycle except the resting phase (G_0) and early G_1 (Kee et al. 2002). Proliferating cell nuclear antigen (PCNA), an auxiliary protein of the DNA polymerase δ occurs in G_1–G_2 with peak expression at the G_1/S interphase and phosphorylated histone H3 is restricted to the G_2 and M-phase of the cell cycle (Galand and Degraef 1989; Hendzel et al. 1997). Such endogenous proliferation markers can be used to confirm that differences in BrdU labeling observed following a procedure are not due to changes in the bioavailability or distribution of exogenous BrdU. To study cell

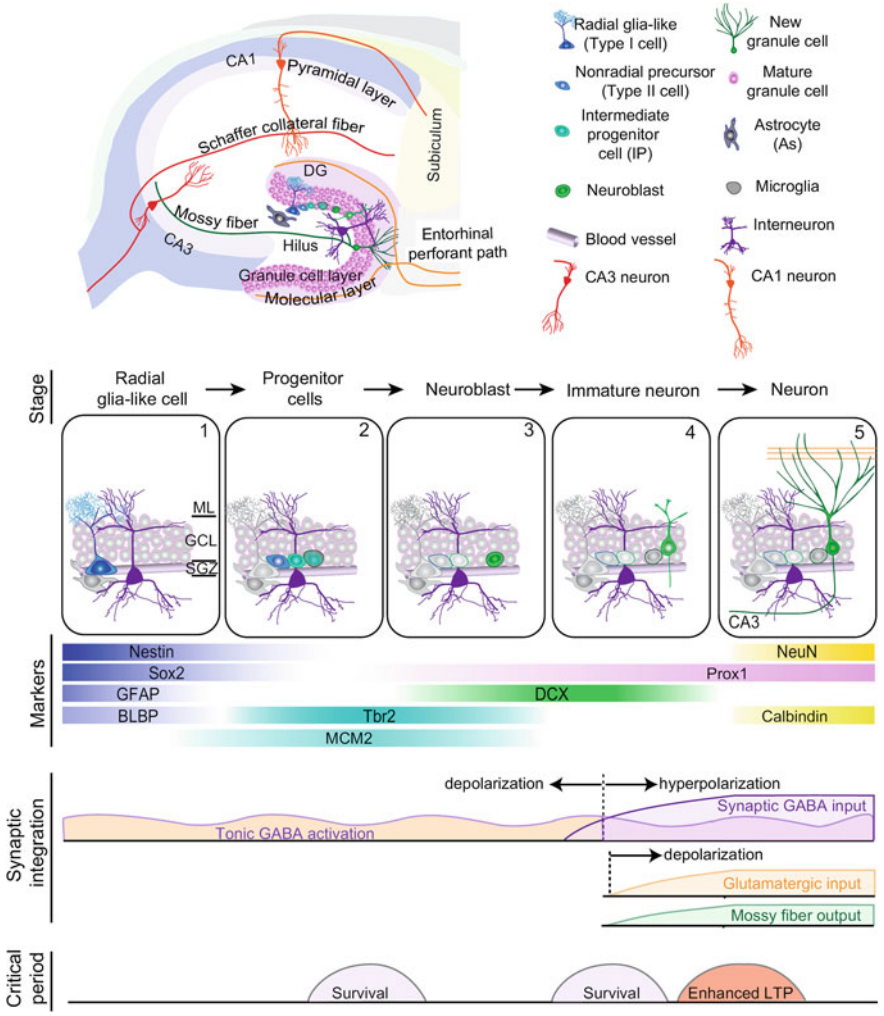

Fig. 1 Overview of adult hippocampal neurogenesis: summary of five developmental stages during adult hippocampal neurogenesis. *1* Activation of quiescent radial glia-like cell in the subgranular zone (*SGZ*). *2* Proliferation of non-radial precursor and intermediate progenitors. *3* Generation of neuroblasts. *4* Integration of immature neurons. *5* Maturation of adult-born neurons. Expression of stage-specific markers, sequential process of synaptic integration, and critical periods regulating survival and plasticity are shown. Dentate gyrus (*DG*), molecular layer (*ML*), granule cell layer (*GCL*), subgranular zone (*SGZ*), glial fibrillary acidic protein (*GFAP*), brain lipid binding protein (*BLMP*), doublecortin (*DCX*), neuronal nuclei (*NeuN*), gamma-aminobutyric acid (*GABA*), and long-term potentiation (*LTP*). Reprinted from Neuron, 70-4, Ming and Song (2011), with permission from Elsevier

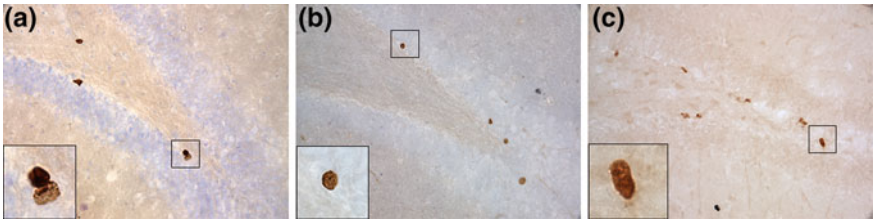

Fig. 2 Representative examples of immunohistochemical analysis for cell proliferation and cell survival in the adult dentate gyrus. Peroxidase staining with DAB as reporter group. 400× magnification, *inserts* 1000×. **a** Cell proliferation of BrdU+ cells, 2 h survival. **b** BrdU+ cell survival (3 weeks). **c** Ki67+ cell proliferation

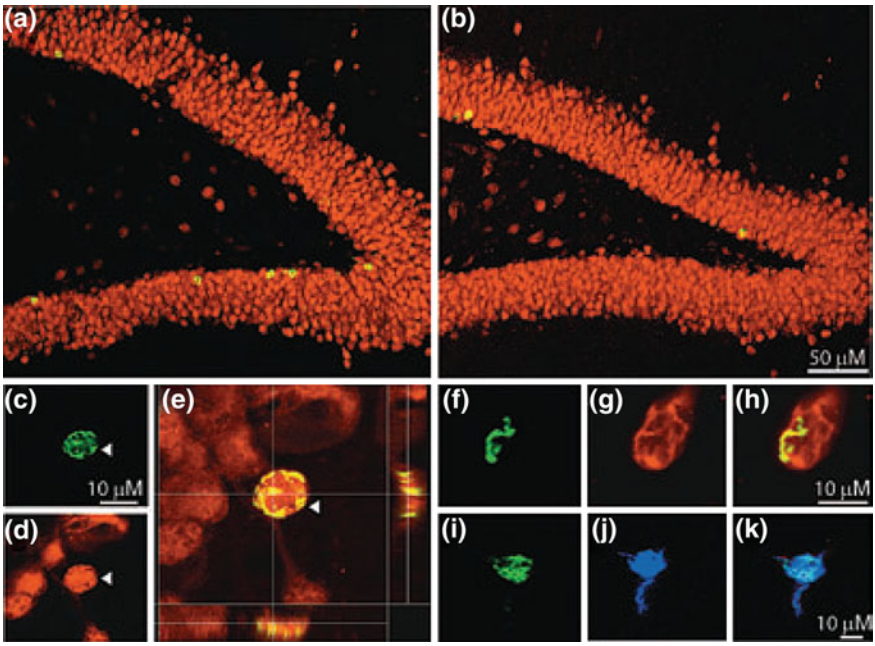

Fig. 3 Confocal images of fluorescence immunolabeling in the dentate gyrus of control (**a**) and sleep deprived (**b**) rats. **a**–**e** Double labeling with BrdU (**c** *green*) and NeuN (**d** *red*), a marker for new neurons. **e** Merged picture of a BrdU+ and NeuN+ cell. **f**–**h** Co-localization of BrdU (**f** *green*) with DCX (**g** *red*). **i**–**k** Co-localization of BrdU (**i** *green*) and S100β (**j** *blue*), a marker for astrocytes. Reprinted from EJN, Guzman-Marin et al. (2005), used with permission from Wiley and Sons

differentiation and maturation of particular phenotypes, newborn cells can be labeled or double-labeled with cell-type specific markers. Commonly used markers include DCX, NeuroD, and TuJ1 for immature neurons, NeuN for mature neurons,

and GFAP or calcium-binding proteins S100, S100β for glial cells (Abrous et al. 2005). See Fig. 3.

4 Regulation and Function of Adult Hippocampal Neurogenesis

Young adult rats produce about 9,000 new cells in the dentate gyrus per day (Cameron and McKay 2001) but the ultimate disposition of new cells is influenced by a wide range of physiological, pathological, and behaviorally mediated stimuli affecting the level of cell proliferation, differentiation, maturation, and survival (Ming and Song 2005). The role of adult-born granule cells in hippocampal function is still under investigation (Song et al. 2012). Participation in learning and memory processes is suggested by the electrophysiological properties of new neurons. Young neurons show robust long-term potentiation (LTP) with a low threshold for LTP induction (Schmidt-Hieber et al. 2004; Ge et al. 2007b). This results in a preferential recruitment of new neurons by behavioral activation (Ramirez-Amaya et al. 2006; Kee et al. 2007). Elimination of hippocampal neurogenesis by irradiation has been shown to severely reduce induction of LTP (Snyder et al. 2001).

Direct tests of a role for new neurons in learning and memory have yielded mixed results. For example, antimitotic drugs can eliminate certain forms of hippocampal-dependent learning, such as trace eye blink conditioning and trace fear conditioning, but not others, such as contextual fear conditioning or spatial navigation learning (Shors et al. 2001, 2002). Nonetheless, a picture is now emerging that adult hippocampal neurogenesis is involved in spatial and temporal pattern separation, trace conditioning, contextual fear conditioning, long-term memory retention, and clearance of hippocampal memory traces (Koehl and Abrous 2011). Importantly, the relationship between adult neurogenesis and learning appears to be reciprocal, because training on these tasks can stimulate cell proliferation or survival (Gould et al. 1999a), as does exposure to enriched environments (Kempermann et al. 1997). An increased pool of new neurons is hypothesized to enhance the capacity for behavioral plasticity, and facilitate adaptation to environmental novelty and complexity (Kempermann 2008).

Hippocampal neurogenesis has also been implicated in the regulation of mood. The hippocampus has reciprocal connections with the amygdala and the prefrontal cortex, and plays a central role in emotions. Stress can precipitate or exacerbate mood disorders, and both major depression and stress are associated with impaired hippocampal function and morphological changes. Negative regulation of neurogenesis by stress (Cameron and Gould 1994; Mirescu and Gould 2006; Hanson et al. 2011), and positive regulation by antidepressant treatments [e.g., SSRIs and exercise; van Praag et al. (1999), Malberg et al. (2000), Leuner et al. (2006), Sahay and Hen (2007)] with a time course mimicking the onset of therapeutic efficacy, suggested a hypothesis that neurogenesis may play a major role in

the pathophysiology and/or recovery from major depression (Jacobs et al. 2000). This hypothesis continues to be explored (Sahay and Hen 2007; Eisch and Petrik 2012; Patricio et al. 2013).

Sleep, like neurogenesis, is implicated in the regulation of memory and mood, and many of the factors that regulate neurogenesis also affect sleep or are affected by sleep. This raises the possibility that sleep may regulate adult neurogenesis, either directly or indirectly, as follows:

1. Sleep may represent a physiological state required for neurogenesis that gates or facilitates critical molecular events in one or more of the stages from cell proliferation to functional neurons. In this relationship, specific events in neurogenesis would occur only during sleep. Sleep would, therefore, be necessary for neurogenesis, and neurogenesis would represent a function of sleep.
2. Sleep may be necessary for maintaining optimal functioning of neural and endocrine processes that in turn regulate neurogenesis. In this relationship, specific events in neurogenesis would not be limited to sleep, but some amount of sleep would be required for neurogenesis to proceed optimally.
3. Sleep disruptions may evoke nonspecific responses such as stress responses or behavioral changes that reduce neurogenesis. In this relationship, sleep would play no special role in neurogenesis, but manipulations of sleep could nonetheless affect the process.

In the following sections, a role for sleep in the regulation of neurogenesis is considered, based on evidence from correlation, deprivation, and stimulation studies.

5 Sleep and Neurogenesis: Correlational Studies

If sleep regulates neurogenesis, then variations in sleep may be paralleled by variations in neurogenesis. In mammals, natural variations in sleep occur across the day (nocturnal and diurnal sleep chronotypes), across the lifespan, and in some species across seasons. One or more processes in neurogenesis could, therefore, vary with time of day, time of year, or time of life.

5.1 Seasonal and Lifespan Correlations

There is a robust correlation between sleep and neurogenesis across the lifespan. Cell proliferation and neurogenesis are maximal during early development when daily sleep amounts are greatest (Alfoldi et al. 1990). The steepest decline in the production of new neurons occurs in the early life stages, likely reflecting a transition of neural stem cells to a quiescent state, resulting in a depletion of the pool of proliferating cells (Lugert et al. 2010; Kempermann 2011b). Cell

proliferation in rodents further declines with age (Heine et al. 2004), although this has not yet been related specifically to changes in sleep parameters.

Seasonal variability in sleep expression occurs in some mammals that migrate or hibernate, but this has not been specifically related to rates of neurogenesis. Neurogenesis in adult birds is beyond the scope of this chapter, but it is worth noting that annual rhythms of neurogenesis and sleep are evident in various avian species. Some species of songbirds each year regrow brain structures necessary for song learning (Barnea and Pravosudov 2011); whether this is associated with variations in sleep has not been directly assessed.

5.2 Correlations with Time of Day

In most mammals, sleep exhibits a prominent daily rhythm driven and synchronized to the solar day by a master retinorecipient circadian clock in the hypothalamic suprachiasmatic nucleus (SCN).

The cell cycle of proliferating cells in the adult rat hippocampus is estimated to be ~24–25 h in duration (Cameron and McKay 2001). If the cell cycle is gated by circadian or sleep–wake dependent factors, then a daily rhythm of cell proliferation should be detectable by comparing BrdU labeling following administration at different times of day. Note that BrdU would be expected to label cells entering the cell cycle beginning 7–9 h (the duration of the S-phase) before its administration. Evidence for a daily rhythm has been obtained using this approach in adult male rats, with four injection times and 2 h post-injection survival time (Guzman-Marin et al. 2007b). BrdU labeling in the granule cell layer/subgranular zone was found to be maximal late in the light (rest) period, with double the number of labeled cells observed when BrdU was administered 9 h after lights-on compared to the beginning of the light period and early or late in the dark period.

Enhanced proliferation near the end of the sleep period is consistent with a neurogenic role for sleep, but other studies have observed either a differently phased rhythm, or no time of day effect (Fig. 4). One study that also used BrdU injections with a 2 h survival time reported 22 % more labeled cells following injections at the end of the dark period relative to the end of the light period (Junek et al. 2010). Another study using the endogenous proliferation marker Ki67 reported a significant rhythm, but with maximum proliferation rates in the middle of the dark period, 6 h after lights-off, and lowest rates in the middle of the light period (Gilhooley et al. 2011). Two studies found no daily variation. In one case, proliferation was measured in single-housed rats using BrdU injections at hours 0 or 9 of the light period, with a 2 h post-injection survival (Mueller et al. 2011). In a second study, BrdU was administered at one of 4-time points but with a 24 h post-injection survival time (Ambrogini et al. 2002). There was no significant effect of time of day, although the longer survival time would likely attenuate time of day differences, depending on how long BrdU remains available, and whether this varies with time of day.

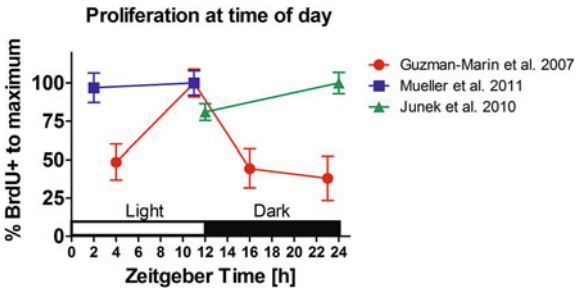

Fig. 4 Circadian variation of cell proliferation in male Sprague–Dawley rats. Replotted data from Guzman-Marin et al. (2007a, b), Mueller et al. (2011) and Junek et al. (2010). Animals were kept in a standard 12:12 h light/dark cycle. Cell proliferation was measures with BrdU and 2 h survival time. X-axis: time of perfusion at Zeitgeber time (ZT, with ZT0 representing light on, as by convention). Guzman-Marin and colleagues reported a circadian variation of cell proliferation with peak levels at the end of the light period. However, the topic remains inconclusive. Neither Mueller et al. (2011) nor Junek et al. (2010) were able to confirm a daily rhythm of adult hippocampal cell proliferation with peak levels of the S-phase at the end of the light period

The cell cycle of proliferating cells in the adult hippocampus of C57BL/6J and BALB/cByJ mice has been estimated to be ~12–14 h (Hayes and Nowakowski 2002) and thus could complete 2 cycles per day, unless progression is stopped in G_0, pending appropriate signals from the circadian clock or sleep-wake states. Three studies reported no daily rhythm of cell proliferation in the granule cell layer/subgranular zone assessed using BrdU or Ki67 in mice housed under sedentary conditions, e.g., without a running wheel (Holmes et al. 2004; Kochman et al. 2006; van der Borght et al. 2006). A fourth study also reported no daily rhythm of BrdU labeling (S-phase), but did find evidence for a daily rhythm of labeling using antibodies to phosphohistone H3 (a marker for M-phase) and phospho cdc2 (marking transition from G2 to M-phase) (Tamai et al. 2008). The authors proposed a model whereby progenitor cells enter the cell cycle at any time of day, but progress through the M-phase primarily at night, producing a nocturnal peak of cell proliferation.

A single study of cell proliferation in the dentate gyrus of the Syrian hamster reported no difference in BrdU labeling following injections at the end of the light period compared to the end of the dark period (Smith et al. 2010). This study used 24 h survival times following injections, which may not be optimal for detecting daily rhythms. Surprisingly, a time of day effect was observed when survival time was extended to 72 h; by contrast with the 24 h survival group, the number of labeled cells in the 72 h survival group was approximately doubled in hamsters that received BrdU at the end of the light period, whereas no increase was seen in hamsters that received BrdU at the end of the dark period. This result implies that cells in the S-phase of mitosis near the end of the light period continue to divide, expanding the number of labeled cells, while those labeled near the end of dark period do not continue to divide, or have reduced survival.

Two studies have reported a significant daily rhythm of BrdU labeling in the hilus, in mice (Kochman et al. 2006) and rats (Guzman-Marin et al. 2007b). In both cases, the peak of labeling was observed following BrdU injections late in the light period. The hilus gives rise primarily to glia cells, thus these results suggest a daily rhythm of hippocampal gliogenesis. Two other rat studies did not detect a rhythm of BrdU labeling in the hilus (Ambrogini et al. 2002; Mueller et al. 2011).

5.3 *Daily Rhythms of Cell Proliferation: Effects of Wheel Running*

Wheel running stimulates cell proliferation and neurogenesis (Vivar et al. 2012). Given that rats and mice are primarily nocturnal runners, free-access to running wheels might be expected to induce a daily rhythm in cell proliferation. A few studies have examined this, again with mixed results. In one study, cell proliferation, cell survival, and the total number of new neurons where all significantly increased relative to sedentary control mice when a running wheel was provided each day for 1 or 3 h at the beginning or in the middle of the dark period, but not when provided in the middle of the light period (Holmes et al. 2004). The mice ran in the wheels at all three times, but more at night, therefore the time of day differences would be consistent with the known effect of exercise on neurogenesis. In that study no daily rhythm of cell proliferation was evident in the sedentary control groups, suggesting that an effect of time of day in mice is likely to be related to waking activity rather than to sleep. A similar result was found using Ki67 as a proliferation marker, with more labeled cells evident near the end of the dark period in mice provided with a running wheel, but not in sedentary controls (van der Borght et al. 2006). One other study observed evidence for a nocturnal peak of proliferation, using a marker for M-phase, but, only in sedentary mice, and not in mice with free-access to a running wheel (Tamai et al. 2008).

5.4 *Summary: Is There a Daily Rhythm of Cell Proliferation in the Hippocampus?*

The available evidence provides no consensus. Of the five rat studies available, two found a rhythm with a nighttime peak, one found a rhythm with a daytime peak, and two found no rhythm. The discrepancy between the Guzman-Marin et al. (2007b) and Mueller et al. (2011) results was unexpected, given that the latter study was modeled closely after the former. A methodological factor that did vary between the two studies was the use of group versus single housing, respectively. Housing conditions have been shown to modulate stress and exercise effects on hippocampal neurogenesis, and possible modulation of time of day effects as well

cannot be ruled out (Stranahan et al. 2006; Kannangara et al. 2009; Leasure and Decker 2009). Of the four mouse studies available, one found evidence for a rhythm with a nighttime peak (Tamai et al. 2008), and three found no rhythm when mice were housed under sedentary conditions (Holmes et al. 2004; Kochman et al. 2006; van der Borght et al. 2006). Three of these studies included a running wheel condition, and, remarkably, the pattern of results across studies was inverted; the one study that reported a daily rhythm under sedentary conditions found no rhythm when a wheel was available (Tamai et al. 2008), while two that reported no rhythm under sedentary conditions obtained evidence consistent with a nighttime peak associated with nocturnal running (Holmes et al. 2004; van der Borght et al. 2006). Finally, four studies have examined time of day effects on cell proliferation in the hilus, with positive evidence in one mouse study (Kochman et al. 2006) and one rat study (Guzman-Marin et al. 2007b), and negative evidence in two other rat studies (Ambrogini et al. 2002; Mueller et al. 2011). The diversity of results does not appear to reflect a species difference, and is more likely to be related to the use of different proliferation markers, injection and survival protocols, and housing conditions. Although consensus is lacking, the results overall are more consistent with regulation of cell proliferation by waking activity rather than by sleep. Ultimately, correlations are silent about causality and must be interpreted in the light of experimental studies employing stimulation and deprivation methods.

6 Sleep and Neurogenesis: Deprivation Studies

If sleep regulates neurogenesis, then sleep disruption should alter the process at one or more levels. Several laboratories have addressed this issue over the last decade. A range of sleep deprivation durations have been evaluated, from 6 h to a week. Most experiments have targeted total sleep deprivation or REM sleep deprivation, but sleep restriction and sleep fragmentation have also been examined. Methods used include gentle handling, exposure to novel objects, forced locomotion, and confinement to a small platform-over water. All of these methods have potential confounds, related to stress and activity levels, which can affect neurogenesis independently of sleep deprivation. Therefore, appropriate control groups are essential to interpret the results. Consistently across studies, sleep deprivation lasting longer than 24 h has been shown to inhibit cell proliferation in the hippocampus, independent of the methodology used or the sleep parameter targeted. Sleep deprivation of less than 24 h may actually increase cell proliferation. Effects on cell survival and maturation have been more variable across studies.

6.1 Short-Term Sleep Deprivation

Short-term sleep deprivation is defined here as procedures that last <2 days, as these appear to affect neurogenesis differently than do longer procedures. Three studies have investigated the effect of 12 h total sleep deprivation during the light phase on cell proliferation in the dorsal dentate gyrus, using BrdU, Ki67, or PCNA as proliferation markers. Two of the studies used rats and reported a significant increase (24 and 38 %, respectively) in cell proliferation using 2 h BrdU labeling (Grassi et al. 2006; Junek et al. 2010). Interpretation is complicated by the observation in one study that despite increased BrdU labeling, there was no change in labeling for the endogenous proliferation markers Ki67 or PCNA (Junek et al. 2010). This was taken to suggest that 12 h total sleep deprivation might transiently accelerate the cell cycle, allowing more dividing cells to enter S-phase (and incorporate BrdU) without increasing the total number of dividing cells (Junek et al. 2010). This is an intriguing hypothesis that merits further study using additional markers of cell cycle phase to measure cycle duration more directly. A study of 12 h total sleep deprivation in mice did not find a change in either 2 h BrdU or Ki67 (van der Borght et al. 2006). As the deprivation and labeling procedures matched those used in the two rat studies, a species difference is possible.

Four studies have examined the effect of 24 h sleep deprivation on BrdU or Ki67 labeling, using procedures for total sleep deprivation (Roman et al. 2005; Junek et al. 2010), REM sleep deprivation (Mirescu et al. 2006), or sleep fragmentation (Guzman-Marin et al. 2007a). Significant effects on cell proliferation or survival in the granule cell layer/subgranular zone were not observed, although one study did report a trend for reduced proliferation in the subgranular zone, and a significant reduction in the hilus (Roman et al. 2005). Also, the sleep fragmentation procedure reduced the number of new cells that expressed neuron-specific markers by ~20 %, indicating an effect on cell differentiation and maturation (Guzman-Marin et al. 2007a).

In addition to 12 and 24 h procedures, Junek et al. (2010) also examined 36 and 48 h total sleep deprivation. The transient increase in BrdU labeling observed following 12 h total sleep deprivation was absent following the other durations, and a trend for reduced cell proliferation was apparent in the 48 h total sleep deprivation group (Junek et al. 2010). One other study did report a significant reduction of cell proliferation in rats after 48 h of total sleep deprivation by gentle handling (Garcia-Garcia et al. 2011). Inhibitory effects of total sleep deprivation on hippocampal cell proliferation thus appear to emerge at about 2 days of sleep loss.

6.2 Long-Term Sleep Deprivation

The first long-term total sleep deprivation studies were conducted using rats and forced locomotion to prevent sleep for 56 h (state-contingent disc-over-water rotation) (Tung et al. 2005) or 96 h (intermittent treadmill) (Guzman-Marin et al. 2003).

By contrast with locomotor control groups, the total sleep deprivation groups showed a reduction of 36 % (Tung et al. 2005) or 54 % (Guzman-Marin et al. 2003) in the basal rate of cell proliferation in the dentate gyrus, assessed by 2 or 48 h BrdU labeling, respectively. EEG recordings confirmed a >90 % reduction in total sleep time, with no REM sleep. Similar results have been obtained in mice using 96 h forced treadmill locomotion and 2 h BrdU labeling, but with a possible strain difference. Proliferation was reduced by 50 % in C57BL6 mice but by <15 % in C3H mice (n.s.) (Sompol et al. 2011). Cell proliferation was rescued in C57 mice but was not affected in C3H mice by administration of *N*-acetyl-serotonin (NAS), a precursor to melatonin that C57 mice lack. This was taken to suggest that endogenous NAS (or melatonin) might protect the neurogenic niche in the C3H strain from inhibitory effects of total sleep deprivation. However, rat strains showing a strong suppression of proliferation by total sleep deprivation are not deficient in NAS or melatonin.

Total sleep deprivation may affect neurogenesis beyond cell proliferation. A study using the 96 h treadmill procedure with 3-week survival after BrdU administration confirmed a 40 % reduction in BrdU labeling, and further reported a 47 % reduction in the proportion of new cells co-labeled with the neuronal marker NeuN (Guzman-Marin et al. 2005). This resulted in a net 60 % reduction of hippocampal neurogenesis, reflecting inhibition of cell proliferation, and a change in cell differentiation, survival, or both.

6.3 Sleep Restriction

Total deprivation of sleep beyond 1 day is presumably rare under natural conditions. By contrast, periods of sleep restriction of varying duration may be quite common, e.g., in shift work, or insomnia. To model chronic sleep restriction, rats were confined to a slowly rotating drum for 20 h/day, for 8 days, with 4 h recovery sleep permitted each day at light onset (Roman et al. 2005). BrdU was administered 5 days prior to sleep restriction. This procedure significantly reduced Ki67 labeling in the hilus and subgranular zone, but the effect in the subgranular zone was not significant by contrast with a forced activity control group, suggesting a nonspecific stress effect. No significant effects were observed in measures of cell survival or maturation, assessed by BrdU and NeuN co-labeling. Similar results were obtained in 30–61 day old adolescent rats subjected to the same 20 h/day sleep restriction procedure for 30 days, using BrdU labeling for cell survival and DCX for maturation (Novati et al. 2011). This study did not include a measure of cell proliferation.

One other study examined the effect of a 6 h/day sleep restriction (gentle handling and exposure to novel objects during the first 6 h of the light period) on neurogenesis stimulated in rats by training on a hippocampal-dependent spatial learning task (Hairston et al. 2005). Rats received two injections of BrdU 7 days prior to 4 days of water maze training. In control rats, training increased both cell survival (total BrdU) and the fraction of new cells expressing the neuronal marker DCX. In sleep-restricted

rats, the training effect on cell survival and neurogenesis was absent, and spatial learning was impaired. These results imply that sleep following training is necessary for spatial learning, and that this may involve a sleep-dependent recruitment (and thus survival) of new neurons. The sleep restriction procedure was also associated with increased CORT, raising the possibility that the effects on neurogenesis and performance were mediated by a nonspecific stress response. The role of stress and CORT in effects of sleep manipulations is discussed further below.

6.4 Sleep Fragmentation

Sleep continuity and the sequences of stages are thought to be important for presumed restorative functions of sleep. Sleep fragmentation is associated with non-restorative sleep, and is characteristic of a variety of common conditions, including obstructive sleep apnea, depression, primary insomnia, and old age (Bonnet and Arand 2003). Two studies have examined the effect of experimental sleep fragmentation on hippocampal neurogenesis. One study confined rats to a treadmill that moved at 10 cm/s for 3 s once every 33 s for 1, 4, or 7 consecutive days (Guzman-Marin et al. 2007a). EEG recordings confirmed highly fragmented sleep characterized by shorter bout duration, increased bout number, a normal amount of NREM sleep, and a ~80 % decrease in REM sleep. Cell proliferation (2 h BrdU or Ki67) was unaffected by the 1 day procedure, but was reduced ~70 % in the 4 and 7 day conditions, compared to treadmill control rats. The proportion of new cells expressing a neuronal phenotype (3-week BrdU+NeuN) was significantly reduced in all 3 conditions. Notably, the 52 % reduction observed in the 4-day sleep fragmentation condition exceeded the 36 % reduction previously observed in rats subjected to 4-day total sleep deprivation (Guzman-Marin et al. 2003). The results leave open the possibility that these effects were mediated by suppression of REM sleep rather than sleep fragmentation.

A second sleep fragmentation study from the same group used a modified treadmill activation protocol to examine effects of sleep fragmentation on neurogenesis and subsequent hippocampal function (Sportiche et al. 2010). The treadmill was actuated for 3 s after 30 consecutive seconds of NREM sleep. This induced sleep fragmentation without altering total daily NREM or REM sleep. BrdU was administered on days 4 and 5 of the 12-day sleep fragmentation procedure, which was followed by 14 days of recovery and 7 days of training on a hippocampus-sensitive Barnes maze spatial learning task. The sleep fragmentation procedure decreased BrdU cell counts by 30 % and impaired performance, but did not decrease the proportion of BrdU-ir cells coexpressing NeuN relative to yoked and treadmill control groups. This latter result suggests that the decrease in the proportion of double-labeled cells observed previously in response to sleep fragmentation (Guzman-Marin et al. 2007a) was due to the suppression of REM sleep caused by the sleep fragmentation procedure. Alternatively, the 7-day training procedure that followed sleep fragmentation may have offered protection.

6.5 REM Sleep Deprivation

Total sleep deprivation and sleep fragmentation procedures leave open the question of whether sleep stages contribute differentially to the suppression of neurogenesis. Selective deprivation of NREM sleep is not possible without affecting REM sleep, because REM sleep is normally entered through NREM sleep. However, a relatively selective REM sleep deprivation can be achieved by state dependent or preemptive deprivation techniques. A classic preemptive REM sleep deprivation method exploits the muscle atonia that accompanies REM sleep. In this procedure, rats or mice are placed on a small platform in a pool of water. Loss of muscle tone at REM sleep onset causes the animal to dip its head toward the water, aborting the episode. This method almost completely suppresses REM sleep, and typically spares 60 % or more of NREM sleep, depending on the duration of the procedure. Multiple platforms can be used to permit social housing and locomotion. Two studies using the platform method reported a consistent 40–50 % reduction of cell proliferation following REM sleep deprivation of 72 h (Mirescu et al. 2006) or 96 h (Mueller et al. 2008). The latter study showed the effect to be independent of the REM sleep deprivation method (single vs. multiple platform), the housing condition (single vs. group housing), the proliferation marker (2 h BrdU vs. Ki67), and the rat strain (Sprague–Dawley vs. Long Evans), and to include both the granule cell layer/subgranular zone and hilus.

A more selective, albeit less complete REM sleep deprivation can be accomplished using a state-contingent deprivation procedure, in which an arousal stimulus is applied after REM sleep is detected. One study used EEG recordings with automated real-time sleep staging to identify REM sleep and actuate a treadmill (Guzman-Marin et al. 2008). Yoked control animals were stimulated at the same time, and allowed to sleep when the REM sleep deprivation animals were spontaneously awake. This method reduced REM sleep by $\sim$80 % in the REM sleep deprivation group relative to yoked and home cage controls. NREM sleep was reduced by only 17 % and NREM EEG slow wave activity was not reduced, as would be expected if there was a homeostatic deficit in this sleep stage. Cell proliferation (BrdU and Ki67) in the dentate gyrus was reduced by 63 % in REM sleep deprivation rats compared to the yoked controls, and across all rats the number of new cells correlated +0.84 with the amount of REM sleep obtained, but only +0.26 with the amount of NREM sleep. These observations support an important role for REM sleep in sustaining basal levels of cell proliferation in the hippocampus.

By contrast with effects on cell proliferation, reported effects of REM sleep deprivation on maturation are less consistent across studies. The two studies that used the platform REM sleep deprivation method reported no effect of 72 or 96 h REM sleep deprivation on the proportion of new cells expressing the neuronal markers TuJ1, NeuN, or DCX (Mirescu et al. 2006; Mueller et al. 2008). However, the 96 h REM sleep deprivation study that used the more selective state-contingent REM sleep deprivation method observed a 30 % reduction in the proportion of new cells co-labeled with NeuN, relative to home cage controls (Guzman-Marin et al. 2008).

The reduction was only 10 % relative to yoked controls, but this likely reflects the 30 % reduction in REM sleep sustained by the yoked controls relative to home cage controls. Although the discrepancy in reported effects on cell maturation remains to be clarified, all three REM sleep deprivation studies are consistent in observing a reduction in cell proliferation comparable to that observed following total sleep deprivation procedures.

6.6 Regional Differences

An important question is whether sleep deprivation affects adult neurogenesis equivalently throughout the brain, or whether the effects are regionally specific. Regional differences could provide clues to the mechanisms by which sleep loss affects neurogenesis, as well as internal controls for nonspecific effects of sleep deprivation procedures that may affect neurogenesis. There appears to be a consensus that cell proliferation in the subventricular zone is not affected by either short-term or long-term sleep deprivation procedures (Grassi et al. 2006; Mirescu et al. 2006; Junek et al. 2010). Therefore, effects of sleep deprivation on proliferation appear to be specific to the hippocampus, similar to other behavioral manipulations known to regulate hippocampal neurogenesis (e.g., training on hippocampal-dependent learning tasks).

6.7 Hippocampal Volume

In humans, several studies have reported a reduction in hippocampal volume, measured by MRI, in various conditions associated with disrupted sleep, including depression (Czeh and Lucassen 2007), sleep apnea (Morrell et al. 2003), and primary insomnia (Riemann et al. 2007; Neylan et al. 2010). One study did not find a volume difference between patients with primary insomnia and good sleepers but did observe a reduced volume in a subgroup of the insomniacs with poor sleep maintenance (Winkelman et al. 2010). Although such decreases in hippocampal volume may not be fully explained by a reduction in neurogenesis alone, it is a reasonable assumption that suppression of neurogenesis may contribute to it (Czeh and Lucassen 2007).

However, sleep deprivation studies in animals do not yet provide supporting evidence. Four day sleep deprivation procedures shown to inhibit cell proliferation by ~50 % did not affect hippocampal volume in rats (Guzman-Marin et al. 2003; Tung et al. 2005; Mueller et al. 2008). Four days is likely too soon to detect volume changes. A 30 day SR study in juvenile rats (4 h sleep/day) did detect a 10 % reduction in hippocampal volume, but did not observe any effects on net survival or differentiation of new neurons, indicating that volume changes were related to other effects (Novati et al. 2011).

6.8 Summary: Effects of Sleep Deprivation

Sleep deprivation for 2 days or longer affects different aspects of hippocampal neurogenesis, independent of the procedure employed. The most consistent effect is on cell proliferation, which is reduced by 50 % or more by total sleep deprivation, REM sleep deprivation, and sleep fragmentation (Fig. 5c). Fragmented sleep appears to be as bad as no sleep for net neurogenesis, but effects of sleep fragmentation on cell phenotype may involve disruption of REM sleep-specific processes. All sleep deprivation procedures have possible confounds such as social isolation, forced locomotion, or stress that can effect hippocampal neurogenesis. The standard use of apparatus or yoked controls, and comparisons between group and single housing deprivation methods, are sufficient to rule out activity and social deprivation as mediators. Stress and disruption of circadian rhythms require more close consideration, and are discussed next in the context of identifying physiological mediators of sleep deprivation effects on neurogenesis.

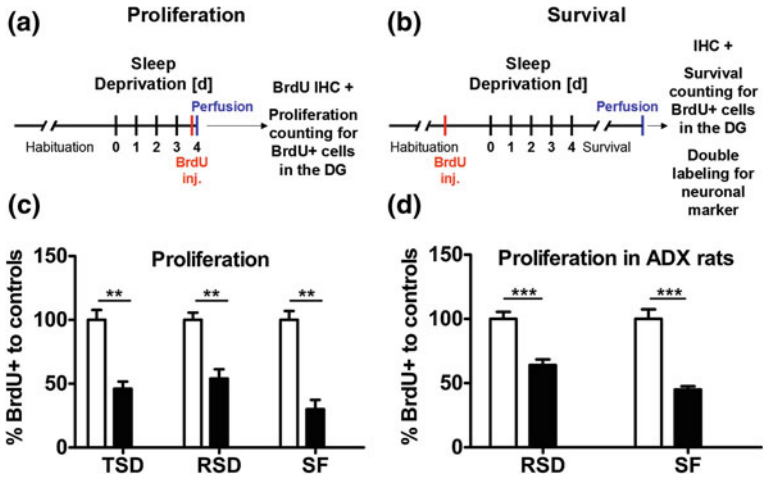

Fig. 5 Summary: sleep deprivation and neurogenesis. **a** Time-line for cell proliferation measurement (BrdU+) after sleep deprivation. **b** Time-line for cell survival and differentiation analysis with sleep deprivation. **c** Sleep deprivation on adult hippocampal cell proliferation in rats. Re-plotted data from: Guzman-Marin et al. (2003), 96-h total sleep deprivation (*TSD*). Mueller et al. (2008), 96-h REM sleep deprivation (*RSD*). Guzman-Marin et al. (Guzman-Marin et al. 2007a, b), 96-h sleep fragmentation (*SF*). TSD, REM, and SF suppressed adult hippocampal cell proliferation (BrdU+) significantly by a similar amount. **d** Sleep deprivation on hippocampal cell proliferation in ADX rats. Replotted data from Mueller et al. (2008), 96-h REM sleep deprivation (*RSD*). Guzman-Marin et al. (2007a, b), sleep fragmentation (*SF*). RSD and SF resulted in a significant reduction of hippocampal cell proliferation in ADX rats, suggesting a CORT-independent pathway

7 Sleep Deprivation: Possible Neuroendocrine and Circadian Mediators

7.1 Adrenal Glucocorticoids

Stress has been defined as any challenge to homeostasis, and by that definition, sleep deprivation is a stressor. Stress is also defined by physiological responses, and is often treated as synonymous with elevated adrenal glucocorticoid corticosterone (CORT) release. Stimuli that elevate CORT can potently inhibit hippocampal neurogenesis, and these effects can be blocked by adrenalectomy (ADX) with low-dose CORT replacement (Mirescu and Gould 2006). Although exceptions to these effects have been noted (Hanson et al. 2011), stress is an obvious potential mediator of sleep deprivation effects on cell proliferation, survival, or maturation.

Sleep deprivation procedures that inhibit neurogenesis have been observed to elevate plasma CORT (Meerlo et al. 2002; Hairston et al. 2005; Mirescu et al. 2006; Mueller et al. 2008). Also, the size of the sleep deprivation effect on proliferation is often greater by contrast with home cage controls than by contrast with apparatus controls (Guzman-Marin et al. 2003, 2008; Roman et al. 2005; Mueller et al. 2008). This suggests that the effect of sleep deprivation on neurogenesis might be driven in part by nonspecific stress.

To evaluate the role of CORT directly, several studies have used ADX to eliminate any CORT response to sleep deprivation (Mirescu et al. 2006; Guzman-Marin et al. 2007a; Mueller et al. 2008). One study found that ADX with low-dose CORT replacement via drinking water eliminated the inhibitory effect of 72 h REM sleep deprivation on cell proliferation, suggesting that the effect of sleep deprivation was CORT dependent (Mirescu et al. 2006). Two other studies found that ADX with low-dose CORT replacement via drinking water (Guzman-Marin et al. 2007a) or via subcutaneous osmotic minipump (Mueller et al. 2008) did not reduce the inhibition of cell proliferation by 4–7 day sleep fragmentation or 96 h REM sleep deprivation, respectively (Fig. 5d). The discrepancy is believed to be due to an interaction between the CORT replacement method and the sleep deprivation method. Mirescu et al. (2006) and Mueller et al. (2008) used the platform-over-water sleep deprivation method, while Guzman-Marin et al. (2007a) used a treadmill sleep fragmentation method. Mueller et al. found that during a 4-day REM sleep deprivation procedure, ADX rats with replacement CORT provided in a water bottle ingested 60 % less CORT than did control animals, due to drinking from the pool, and these REM sleep deprivation rats did not exhibit a significant decrease in cell proliferation compared to ADX cage controls. The rats in Guzman et al. did not have an alternative source of water. If ADX rats do not receive sufficient CORT, cell proliferation increases (Cameron and Gould 1994). The ADX rats in Mirescu et al. (2006) may have consumed less CORT during sleep deprivation than the control group, inducing upregulation of cell proliferation sufficient to offset an inhibitory effect of REM sleep deprivation.

In summary, while sleep deprivation is mildly to moderately stressful, elevated levels of CORT are not required for sleep deprivation to inhibit cell proliferation in rats. However, elevated CORT is sufficient to suppress cell proliferation (see Sect. 7.2), and may contribute to observed deficits, as suggested by a larger effect size of sleep fragmentation on cell proliferation in intact rats compared to ADX rats (−70 % vs. −55 %) (Guzman-Marin et al. 2007a). Additional studies are needed to determine if CORT might contribute to the inhibitory effects of sleep deprivation on neuronal differentiation and survival.

7.2 Cytokines

ADX eliminates the CORT response to stressors, but other correlates of stress may remain. Interleukins, usually produced by microglia, are abundant in the brain after various stressors. Neuroinflammation and the cytokines IL6 and TNFα have been shown to decrease neurogenesis in vivo and in vitro (Vallieres et al. 2002; Ekdahl et al. 2003; Monje et al. 2003). Furthermore, IL1β activation and subsequent NFκB signaling have been proposed to mediate the inhibitory effects of acute and chronic stress on cell proliferation in the hippocampus (Goshen et al. 2008; Koo and Duman 2008; Koo et al. 2010). Importantly, the cytokines IL1β, TNFα, and IL6 are elevated after sleep deprivation and chronic sleep disturbances, similar to activation after other stressors (Everson 2005; Irwin et al. 2006; Yehuda et al. 2009). This effect might be enhanced in ADX animals, given evidence that CORT regulates proinflammatory cytokines by negative feedback (Nguyen et al. 1998). Direct evidence that proinflammatory cytokines mediate the effect of sleep deprivation on neurogenesis is still lacking. To evaluate a role for the cytokine IL1β, wildtype (WT) and IL1 receptor knockout (IL1R-KO) mice, with or without ADX, were subjected to the 3-day platform-over-water REM sleep deprivation procedure (Mueller and Mistlberger 2013). REM sleep deprivation significantly inhibited cell proliferation (2 h BrdU, Ki67) in IL1R-KO and WT ADX mice, but not in IL1R-KO mice with ADX. These data suggest that REM sleep deprivation can inhibit cell proliferation by activating proinflammatory cytokines or by adrenal CORT release. This further implies that IL1β and CORT affect cell proliferation via parallel molecular pathways, consistent with other observations (Koo et al. 2010).

7.3 Growth Factors

Exogenous growth hormone (GH) was found to increase hippocampal cell proliferation by ∼300 % in rats and to block the inhibitory effect of 48 h of total sleep deprivation by comparison with saline-treated total sleep deprivation rats (Garcia-Garcia et al. 2011). However, by comparison with control rats receiving GH, the total sleep deprivation rats receiving GH had only one third the number of

new cells. Evidently, total sleep deprivation can suppress cell proliferation even in the presence of high levels of GH. This implies that suppression of sleep-associated GH release does not mediate the inhibitory effects of sleep deprivation on cell proliferation.

Brain-derived neurotrophic factor (BDNF) also stimulates neurogenesis (Lee et al. 2002; Scharfman et al. 2005). Hippocampal BDNF was reduced after 48 h sleep deprivation by intermittent treadmill activation, and this reduction correlated with loss of REM sleep (Guzman-Marin et al. 2006). Inhibition of cell proliferation by REM sleep deprivation also correlated with the degree of REM sleep suppression (Guzman-Marin et al. 2008). Whether BDNF replacement can reverse the effect of sleep deprivation on neurogenesis remains to be examined.

7.4 Serotonin

Serotonin induces hippocampal cell proliferation in part via $5HT_{1A}$ receptors (Radley and Jacobs 2002; Banasr et al. 2004). Serotonin neurons in the dorsal raphe innervate the hippocampus, are active during waking and quiescent during sleep (Portas et al. 2000). Chronic sleep restriction might, therefore, be expected to enhance cell proliferation by increased serotonergic stimulation. However, sleep deprivation has been shown to desensitize the $5HT_{1A}$ receptor system, with a time course similar to the antineurogenic effect of prolonged sleep restriction (Novati et al. 2008). Thus, reduced serotonergic signaling during sleep loss may contribute to suppression of cell proliferation. Alterations in neurotransmitter signaling by sleep loss merits further study.

7.5 Disrupted Circadian Rhythmicity and Hippocampal Neurogenesis

Total sleep deprivation necessarily eliminates daily sleep-wake rhythms, and often also disrupts daily rhythms of activity, eating, drinking, body temperature, and sleep-wake dependent neural and endocrine variables. A 4-day REM sleep deprivation procedure was also found to significantly attenuate daily rhythms of locomotion, wake and drinking activity (Mueller et al. 2008). Sleep fragmentation procedures attenuate daily rhythms without suppressing total sleep time, and inhibit neurogenesis to the same degree as total sleep deprivation (Guzman-Marin et al. 2007a; Sportiche et al. 2010). This raises the possibility that the anti-neurogenic effects of sleep loss are secondary to disruptions of the circadian organization of sleep-wake or of factors known to regulate neurogenesis. So far, evidence for this is mixed. Attenuation or loss of circadian rhythms by 4 days or 1 month of exposure to bright light did not suppress cell proliferation in rats

(Mueller et al. 2011). However, repeated shifting of the LD cycle can suppress cell proliferation and survival in the hippocampus (Gibson et al. 2010; Kott et al. 2012). It is possible that an abnormal phase alignment of circadian rhythms induced by repeated shifting is worse than having no circadian rhythms at all. A mechanism for such an effect is unknown, but there is precedence for this idea from studies of circadian rhythms and longevity (Pittendrigh and Minis 1972; Oklejewicz and Daan 2002; Wyse et al. 2010). LD shift studies so far have not included polysomnographic sleep assessments so it is not known whether the effects are due to circadian disruption or changes in sleep.

7.6 Summary of Potential Mechanism

Effects of sleep deprivation on different stages of neurogenesis may be mediated by neuronal, neuroendocrine and immune factors, which may make different contributions depending on the type and duration of sleep disruption. The possibility that stress related increases in plasma CORT and IL1b are necessary and sufficient for sleep deprivation effects on cell proliferation, suggested by the results of one REM sleep deprivation study (Mueller and Mistlberger 2013), needs to be evaluated using other sleep deprivation procedures. A possible contribution of circadian organization also merits further attention.

8 Sleep Stimulation Studies

If sleep promotes neurogenesis, then procedures that enhance sleep, either acutely or chronically, may enhance neurogenesis. Sleep can be induced pharmacologically, with the proviso that hypnotics may not simulate natural sleep processes. Sleep can also be enhanced by prior restriction, raising the possibility of sleep-dependent compensatory increases in aspects of neurogenesis, if prior restriction acutely suppresses neurogenesis.

8.1 Sleep Increases After Sleep Deprivation

Sleep duration and intensity show compensatory increases after sleep deprivation. Two studies found that 6–8 h of recovery sleep did not increase cell proliferation over the low levels observed immediately following 48–72 h REM sleep deprivation (Tung et al. 2005; Mirescu et al. 2006). However, after a week of recovery from 72 h REM sleep deprivation, the number of BrdU-labeled cells was enhanced by 68 % over control rates (Mirescu et al. 2006). This “overshoot of new neurons” was also evident in a REM sleep deprivation-adrenalectomized group that did not

exhibit decreased cell proliferation. Therefore, something other than reduced cell proliferation is sufficient to enhance cell survival. Recovery sleep was not measured during the week after sleep deprivation, but extra sleep can continue to accumulate for several days after sleep deprivation (Mistlberger et al. 1983), and REM sleep rebounds can persist for weeks after long-term REM sleep deprivation (Everson et al. 1989). This leaves open the possibility that a period of increased total sleep or REM sleep promotes cell survival.

In Mirescu et al. (2006), increased cell survival was not evident after 2 weeks recovery, suggesting a subsequent downregulation of cell survival. One study did report increased cell survival and neuronal phenotypes at this time point after a 48 h total sleep deprivation (Garcia-Garcia et al. 2011), while others have reported a reduction in net neurogenesis 3 weeks after sleep deprivation procedures (Guzman-Marin et al. 2005, 2008). Additional work will be needed to clarify the dynamics of recovery from sleep deprivation and potential relationships with recovery sleep parameters.

8.2 Hypnotics

The neurotransmitter GABA regulates survival and maturation of proliferating adult-born hippocampal neurons. Hypnotic drugs enhance sleep via actions on GABA receptors. Two studies have evaluated hippocampal neurogenesis in rats following acute and long-term treatment with the nonbenzodiazepine hypnotics zolpidem (Takase et al. 2009) and eszopiclone (Methippara et al. 2010), administered during the daily light (sleep) period to mimic normal use in humans. Zolpidem inhibited cell proliferation after 2 days treatment, but had no effect on either proliferation or survival after 21 days treatment, suggesting a delayed compensatory effect, and no net benefit. In one study, eszopiclone had no effect on proliferation after 7 days treatment, but increased cell survival by 46 % after 2 weeks treatment. Increments in sleep time were modest or absent, suggesting that any effects of the drugs were due to direct actions on GABA receptors rather than changes in sleep (Methippara et al. 2010). A third study reported no effect of 21 day treatments with eszopiclone or fluoxetine alone, but a significant increase in cell survival to combined treatment (Su et al. 2009).

8.3 Postprandial Sleep

In rodents, sleep occurs naturally following feeding. Postprandial sleep can be enhanced by restricting food availability to a single large daily meal. This technique was used to evaluate sleep effects on the survival of adult-born neurons in the olfactory bulb and the dentate gyrus. In the olfactory bulb, a significant proportion of new granule cells are eliminated by caspase-mediated apoptosis,

a process that is upregulated by olfactory deprivation. Using mice, a peak of apoptosis was found to occur during the 2 h immediately following a fixed daily meal and to correlate with the amount of postprandial sleep (Yokoyama et al. 2011). This did not depend on the time of day of feeding, and was also observed following postprandial sleep in *adlib* fed mice. However, the effect was specific to the olfactory bulb, and not evident in the dentate gyrus, which is at odds with the findings that sleep deprivation primarily affects neurogenesis in the hippocampus.

9 Conclusions

This review has identified possible relationships between sleep and hippocampal neurogenesis, and examined whether the apparent role of sleep in hippocampal functions might reflect in part a role for sleep in the regulation of adult neurogenesis. The evidence from correlational, deprivation, and stimulation studies is complex and does not yet permit definitive conclusions. Importantly, while the studies discussed have assessed effects of sleep deprivation or disturbance on hippocampal cell proliferation, differentiation, and survival, one crucial aspect in the generation of new neurons has not yet been looked at, that is, how sleep deprivation affects the formation of synapses and the integration of new cells in the hippocampal network. The strongest statement that can be made at present is that any disruption of sleep extended beyond 1 day is likely to impair the process of neurogenesis in the hippocampus. These effects may be mediated by any of several pathways, involving glucocorticoids, proinflammatory cytokines, and neurotransmitters. It is not clear that critical steps in neurogenesis are gated by sleep, but it is very likely that sleep is required to maintain functioning of neural systems (e.g., serotonin) that regulate hippocampal neurogenesis. Ultimately, impaired neurogenesis may underlie memory and mood effects associated with acute and chronic sleep disruptions.

References

Abrous DN, Koehl M, Le MM (2005) Adult neurogenesis: from precursors to network and physiology. Physiol Rev 85:523–569

Alfoldi P, Tobler I, Borbely AA (1990) Sleep regulation in rats during early development. Am J Physiol 258:R634–R644

Altman J (1969) Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 137:433–457

Altman J, Das GD (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 124:319–335

Ambrogini P, Orsini L, Mancini C, Ferri P, Barbanti I, Cuppini R (2002) Persistently high corticosterone levels but not normal circadian fluctuations of the hormone affect cell proliferation in the adult rat dentate gyrus. Neuroendocrinology 76:366–372

Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 29:450–460

Barnea A, Pravosudov V (2011) Birds as a model to study adult neurogenesis: bridging evolutionary, comparative and neuroethological approaches. Eur J Neurosci 34:884–907

Bonfanti L, Peretto P (2011) Adult neurogenesis in mammals—a theme with many variations. Eur J Neurosci 34:930–950

Bonnet MH, Arand DL (2003) Clinical effects of sleep fragmentation versus sleep deprivation. Sleep Med Rev 7:297–310

Cameron HA, Gould E (1994) Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. Neuroscience 61:203–209

Cameron HA, McKay RD (2001) Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 435:406–417

Cameron HA, Woolley CS, McEwen BS, Gould E (1993) Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. Neuroscience 56:337–344

Czeh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? Eur Arch Psychiatry Clin Neurosci 257:250–260

Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA (2003) Short-term and long-term survival of new neurons in the rat dentate gyrus. J Comp Neurol 460:563–572

Eisch AJ, Petrik D (2012) Depression and hippocampal neurogenesis: a road to remission? Science 338:72–75

Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O (2003) Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A 100:13632–13637

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313–1317

Everson CA (2005) Clinical assessment of blood leukocytes, serum cytokines, and serum immunoglobulins as responses to sleep deprivation in laboratory rats. Am J Physiol Regul Integr Comp Physiol 289:R1054–R1063

Everson CA, Gilliland MA, Kushida CA, Pilcher JJ, Fang VS, Refetoff S, Bergmann BM, Rechtschaffen A (1989) Sleep deprivation in the rat: IX. Recovery. Sleep 12:60–67

Galand P, Degraef C (1989) Cyclin/PCNA immunostaining as an alternative to tritiated thymidine pulse labelling for marking S phase cells in paraffin sections from animal and human tissues. Cell Tissue Kinet 22:383–392

Garcia-Garcia F, De la Herran-Arita AK, Juarez-Aguilar E, Regalado-Santiago C, Millan-Aldaco D, Blanco-Centurion C, Drucker-Colin R (2011) Growth hormone improves hippocampal adult cell survival and counteracts the inhibitory effect of prolonged sleep deprivation on cell proliferation. Brain Res Bull 84:252–257

Ge S, Pradhan DA, Ming GL, Song H (2007a) GABA sets the tempo for activity-dependent adult neurogenesis. Trends Neurosci 30:1–8

Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007b) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559–566

Gibson EM, Wang C, Tjho S, Khattar N, Kriegsfeld LJ (2010) Experimental 'jet lag' inhibits adult neurogenesis and produces long-term cognitive deficits in female hamsters. PLoS ONE 5:e15267

Gilhooley MJ, Pinnock SB, Herbert J (2011) Rhythmic expression of per1 in the dentate gyrus is suppressed by corticosterone: implications for neurogenesis. Neurosci Lett 489:177–181

Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, Yirmiya R (2008) Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Mol Psychiatry 13:717–728

Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ (1999a) Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 2:260–265

Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E (1999b) Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci U S A 96:5263–5267

Grassi ZG, Cipriani S, Balgkouranidou I, Scattoni R (2006) 'One night' sleep deprivation stimulates hippocampal neurogenesis. Brain Res Bull 69:375–381

Gratzner HG (1982) Monoclonal antibody to 5-bromo- and 5-iododeoxyuridine: a new reagent for detection of DNA replication. Science 218:474–475

Gu Y, Arruda-Carvalho M, Wang J, Janoschka SR, Josselyn SA, Frankland PW, Ge S (2012) Optical controlling reveals time-dependent roles for adult-born dentate granule cells. Nat Neurosci 15:1700–1706

Guzman-Marin R, Bashir T, Suntsova N, Szymusiak R, McGinty D (2007a) Hippocampal neurogenesis is reduced by sleep fragmentation in the adult rat. Neuroscience 148:325–333

Guzman-Marin R, Suntsova N, Bashir T, Nienhuis R, Szymusiak R, McGinty D (2008) Rapid eye movement sleep deprivation contributes to reduction of neurogenesis in the hippocampal dentate gyrus of the adult rat. Sleep 31:167–175

Guzman-Marin R, Suntsova N, Bashir T, Szymusiak R, McGinty D (2007b) Cell proliferation in the dentate gyrus of the adult rat fluctuates with the light-dark cycle. Neurosci Lett 422:198–201

Guzman-Marin R, Suntsova N, Methippara M, Greiffenstein R, Szymusiak R, McGinty D (2005) Sleep deprivation suppresses neurogenesis in the adult hippocampus of rats. Eur J Neurosci 22:2111–2116

Guzman-Marin R, Suntsova N, Stewart DR, Gong H, Szymusiak R, McGinty D (2003) Sleep deprivation reduces proliferation of cells in the dentate gyrus of the hippocampus in rats. J Physiol 549:563–571

Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol 575:807–819

Hairston IS, Little MT, Scanlon MD, Barakat MT, Palmer TD, Sapolsky RM, Heller HC (2005) Sleep restriction suppresses neurogenesis induced by hippocampus-dependent learning. J Neurophysiol 94:4224–4233

Hanson ND, Owens MJ, Nemeroff CB (2011) Depression, antidepressants, and neurogenesis: a critical reappraisal. Neuropsychopharmacology 36:2589–2602

Hayes NL, Nowakowski RS (2002) Dynamics of cell proliferation in the adult dentate gyrus of two inbred strains of mice. Brain Res Dev Brain Res 134:77–85

Heine VM, Maslam S, Joels M, Lucassen PJ (2004) Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus-pituitary-adrenal axis activation. Neurobiol Aging 25:361–375

Hendzel MJ, Wei Y, Mancini MA, Van HA, Ranalli T, Brinkley BR, Bazett-Jones DP, Allis CD (1997) Mitosis-specific phosphorylation of histone H3 initiates primarily within pericentromeric heterochromatin during G2 and spreads in an ordered fashion coincident with mitotic chromosome condensation. Chromosoma 106:348–360

Holmes MM, Galea LA, Mistlberger RE, Kempermann G (2004) Adult hippocampal neurogenesis and voluntary running activity: circadian and dose-dependent effects. J Neurosci Res 76:216–222

Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S (2006) Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med 166:1756–1762

Jacobs BL, van Praag H, Gage FH (2000) Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 5:262–269

Junek A, Rusak B, Semba K (2010) Short-term sleep deprivation may alter the dynamics of hippocampal cell proliferation in adult rats. Neuroscience 170:1140–1152

Kannangara TS, Webber A, Gil-Mohapel J, Christie BR (2009) Stress differentially regulates the effects of voluntary exercise on cell proliferation in the dentate gyrus of mice. Hippocampus 19:889–897

Kaplan MS, Hinds JW (1977) Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. Science 197:1092–1094

Kee N, Sivalingam S, Boonstra R, Wojtowicz JM (2002) The utility of Ki-67 and BrdU as proliferative markers of adult neurogenesis. J Neurosci Methods 115:97–105

Kee N, Teixeira CM, Wang AH, Frankland PW (2007) Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. Nat Neurosci 10:355–362

Kempermann G (2011a) Seven principles in the regulation of adult neurogenesis. Eur J Neurosci 33:1018–1024

Kempermann G (2008) The neurogenic reserve hypothesis: what is adult hippocampal neurogenesis good for? Trends Neurosci 31:163–169

Kempermann G (2011b) The pessimist's and optimist's views of adult neurogenesis. Cell 145:1009–1011

Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. Nature 386:493–495

Kochman LJ, Weber ET, Fornal CA, Jacobs BL (2006) Circadian variation in mouse hippocampal cell proliferation. Neurosci Lett 406:256–259

Koehl M, Abrous DN (2011) A new chapter in the field of memory: adult hippocampal neurogenesis. Eur J Neurosci 33:1101–1114

Koo JW, Duman RS (2008) IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci USA 105:751–756

Koo JW, Russo SJ, Ferguson D, Nestler EJ, Duman RS (2010) Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. Proc Natl Acad Sci USA 107:2669–2674

Kott J, Leach G, Yan L (2012) Direction-dependent effects of chronic "jet-lag" on hippocampal neurogenesis. Neurosci Lett 515:177–180

Leasure JL, Decker L (2009) Social isolation prevents exercise-induced proliferation of hippocampal progenitor cells in female rats. Hippocampus 19:907–912

Lee DA, Blackshaw S (2012) Functional implications of hypothalamic neurogenesis in the adult mammalian brain. Int J Dev Neurosci 30(8):615–621

Lee J, Duan W, Mattson MP (2002) Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 82:1367–1375

Leuner B, Gould E, Shors TJ (2006) Is there a link between adult neurogenesis and learning? Hippocampus 16:216–224

Lledo PM, Alonso M, Grubb MS (2006) Adult neurogenesis and functional plasticity in neuronal circuits. Nat Rev Neurosci 7:179–193

Lois C, Alvarez-Buylla A (1994) Long-distance neuronal migration in the adult mammalian brain. Science 264:1145–1148

Lugert S, Basak O, Knuckles P, Haussler U, Fabel K, Gotz M, Haas CA, Kempermann G, Taylor V, Giachino C (2010) Quiescent and active hippocampal neural stem cells with distinct morphologies respond selectively to physiological and pathological stimuli and aging. Cell Stem Cell 6:445–456

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110

Manganas LN, Zhang X, Li Y, Hazel RD, Smith SD, Wagshul ME, Henn F, Benveniste H, Djuric PM, Enikolopov G, Maletic-Savatic M (2007) Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science 318:980–985

Markakis EA, Gage FH (1999) Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. J Comp Neurol 406:449–460

Meerlo P, Koehl M, van der Borght K, Turek FW (2002) Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. J Neuroendocrinol 14:397–402

Methippara M, Bashir T, Suntsova N, Szymusiak R, McGinty D (2010) Hippocampal adult neurogenesis is enhanced by chronic eszopiclone treatment in rats. J Sleep Res 19:384–393
Ming GL, Song H (2005) Adult neurogenesis in the mammalian central nervous system. Annu Rev Neurosci 28:223–250
Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70:687–702
Mirescu C, Gould E (2006) Stress and adult neurogenesis. Hippocampus 16:233–238
Mirescu C, Peters JD, Noiman L, Gould E (2006) Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glucocorticoids. Proc Natl Acad Sci U S A 103:19170–19175
Mistlberger RE, Bergmann BM, Waldenar W, Rechtschaffen A (1983) Recovery sleep following sleep deprivation in intact and suprachiasmatic nuclei-lesioned rats. Sleep 6:217–233
Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. Science 302:1760–1765
Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR (2003) Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 4:451–454
Mueller AD, Mear RJ, Mistlberger RE (2011) Inhibition of hippocampal neurogenesis by sleep deprivation is independent of circadian disruption and melatonin suppression. Neuroscience 193:170–181
Mueller AD, Mistlberger RE (2013) Inhibition of hippocampal cell proliferation by sleep deprivation in adult mice requires either interleukin-1 receptor signaling or elevated corticosterone. Brain Behav Immun doi:pii:S0889-1591(13)00500-X.10.1016/j.bbi.2013.10.001
Mueller AD, Pollock MS, Lieblich SE, Epp JR, Galea LA, Mistlberger RE (2008) Sleep deprivation can inhibit adult hippocampal neurogenesis independent of adrenal stress hormones. Am J Physiol Regul Integr Comp Physiol 294:R1693–R1703
Neylan TC, Mueller SG, Wang Z, Metzler TJ, Lenoci M, Truran D, Marmar CR, Weiner MW, Schuff N (2010) Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. Biol Psychiatry 68:494–496
Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, Maier SF (1998) Exposure to acute stress induces brain interleukin-1beta protein in the rat. J Neurosci 18:2239–2246
Novati A, Hulshof HJ, Koolhaas JM, Lucassen PJ, Meerlo P (2011) Chronic sleep restriction causes a decrease in hippocampal volume in adolescent rats, which is not explained by changes in glucocorticoid levels or neurogenesis. Neuroscience 190:145–155
Novati A, Roman V, Cetin T, Hagewoud R, den Boer JA, Luiten PG, Meerlo P (2008) Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. Sleep 31:1579–1585
Oklejewicz M, Daan S (2002) Enhanced longevity in tau mutant Syrian hamsters, Mesocricetus auratus. J Biol Rhythms 17:210–216
Palmer TD, Willhoite AR, Gage FH (2000) Vascular niche for adult hippocampal neurogenesis. J Comp Neurol 425:479–494
Paton JA, Nottebohm FN (1984) Neurons generated in the adult brain are recruited into functional circuits. Science 225:1046–1048
Patricio P, Mateus-Pinheiro A, Sousa N, Pinto L (2013) Re-cycling paradigms: cell cycle regulation in adult hippocampal neurogenesis and implications for depression. Mol Neurobiol 48:84–96
Pittendrigh CS, Minis DH (1972) Circadian systems: longevity as a function of circadian resonance in Drosophila melanogaster. Proc Natl Acad Sci U S A 69:1537–1539
Portas CM, Bjorvatn B, Ursin R (2000) Serotonin and the sleep/wake cycle: special emphasis on microdialysis studies. Prog Neurobiol 60:13–35
Radley JJ, Jacobs BL (2002) 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res 955:264–267
Ramirez-Amaya V, Marrone DF, Gage FH, Worley PF, Barnes CA (2006) Integration of new neurons into functional neural networks. J Neurosci 26:12237–12241
Reynolds BA, Weiss S (1992) Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255:1707–1710

Riemann D, Voderholzer U, Spiegelhalder K, Hornyak M, Buysse DJ, Nissen C, Hennig J, Perlis ML, van Elst LT, Feige B (2007) Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. Sleep 30:955–958

Roman V, van der Borght K, Leemburg SA, Van der Zee EA, Meerlo P (2005) Sleep restriction by forced activity reduces hippocampal cell proliferation. Brain Res 1065:53–59

Sahay A, Hen R (2007) Adult hippocampal neurogenesis in depression. Nat Neurosci 10:1110–1115

Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S (2005) Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 192:348–356

Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429:184–187

Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E (2001) Neurogenesis in the adult is involved in the formation of trace memories. Nature 410:372–376

Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E (2002) Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 12:578–584

Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 7:483–495

Smith JM, Hechtman A, Swann J (2010) Fluctuations in cellular proliferation across the light/dark cycle in the subgranular zone of the dentate gyrus in the adult male Syrian hamster. Neurosci Lett 473:192–195

Snyder JS, Kee N, Wojtowicz JM (2001) Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol 85:2423–2431

Sompol P, Liu X, Baba K, Paul KN, Tosini G, Iuvone PM, Ye K (2011) N-acetylserotonin promotes hippocampal neuroprogenitor cell proliferation in sleep-deprived mice. Proc Natl Acad Sci U S A 108:8844–8849

Song J, Christian K, Ming GL, Song H (2012) Modification of hippocampal circuitry by adult neurogenesis. Dev Neurobiol 72(7):1032–1043

Sportiche N, Suntsova N, Methippara M, Bashir T, Mitrani B, Szymusiak R, McGinty D (2010) Sustained sleep fragmentation results in delayed changes in hippocampal-dependent cognitive function associated with reduced dentate gyrus neurogenesis. Neuroscience 170:247–258

Stanfield BB, Trice JE (1988) Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp Brain Res 72:399–406

Stranahan AM, Khalil D, Gould E (2006) Social isolation delays the positive effects of running on adult neurogenesis. Nat Neurosci 9:526–533

Su XW, Li XY, Banasr M, Duman RS (2009) Eszopiclone and fluoxetine enhance the survival of newborn neurons in the adult rat hippocampus. Int J Neuropsychopharmacol 12:1421–1428

Takase LF, Fornal CA, Jacobs BL (2009) Effects of the hypnotic drug zolpidem on cell proliferation and survival in the dentate gyrus of young and old rats. Brain Res 1259:26–31

Tamai S, Sanada K, Fukada Y (2008) Time-of-day-dependent enhancement of adult neurogenesis in the hippocampus. PLoS ONE 3:e3835

Tashiro A, Makino H, Gage FH (2007) Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 27:3252–3259

Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH (2006) NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. Nature 442:929–933

Taupin P (2007) BrdU immunohistochemistry for studying adult neurogenesis: paradigms, pitfalls, limitations, and validation. Brain Res Rev 53:198–214

Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH (2007) Synapse formation on neurons born in the adult hippocampus. Nat Neurosci 10:727–734

Tozuka Y, Fukuda S, Namba T, Seki T, Hisatsune T (2005) GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells. Neuron 47:803–815

Tung A, Takase L, Fornal C, Jacobs B (2005) Effects of sleep deprivation and recovery sleep upon cell proliferation in adult rat dentate gyrus. Neuroscience 134:721–723

Vallieres L, Campbell IL, Gage FH, Sawchenko PE (2002) Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. J Neurosci 22:486–492

van der Borght K, Ferrari F, Klauke K, Roman V, Havekes R, Sgoifo A, Van der Zee EA, Meerlo P (2006) Hippocampal cell proliferation across the day: increase by running wheel activity, but no effect of sleep and wakefulness. Behav Brain Res 167:36–41

van Praag H, Kempermann G, Gage FH (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 2:266–270

van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH (2002) Functional neurogenesis in the adult hippocampus. Nature 415:1030–1034

Vivar C, Potter MC, van Praag H (2012) All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. Curr Top Behav Neurosci 15:189–210

Winkelman JW, Benson KL, Buxton OM, Lyoo IK, Yoon S, O'Connor S, Renshaw PF (2010) Lack of hippocampal volume differences in primary insomnia and good sleeper controls: an MRI volumetric study at 3 Tesla. Sleep Med 11:576–582

Wyse CA, Coogan AN, Selman C, Hazlerigg DG, Speakman JR (2010) Association between mammalian lifespan and circadian free-running period: the circadian resonance hypothesis revisited. Biol Lett 6:696–698

Yehuda S, Sredni B, Carasso RL, Kenigsbuch-Sredni D (2009) REM sleep deprivation in rats results in inflammation and interleukin-17 elevation. J Interferon Cytokine Res 29:393–398

Yokoyama TK, Mochimaru D, Murata K, Manabe H, Kobayakawa K, Kobayakawa R, Sakano H, Mori K, Yamaguchi M (2011) Elimination of adult-born neurons in the olfactory bulb is promoted during the postprandial period. Neuron 71:883–897

Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 26:3–11

Animal Studies on the Role of Sleep in Memory: From Behavioral Performance to Molecular Mechanisms

Robbert Havekes, Peter Meerlo and Ted Abel

Abstract Although the exact functions of sleep remain a topic of debate, several hypotheses propose that sleep benefits neuronal plasticity, which ultimately supports brain function and cognition. For over a century, researchers have applied a wide variety of behavioral, electrophysiological, biochemical, and molecular approaches to study how memory processes are promoted by sleep and perturbed by sleep loss. Interestingly, experimental studies indicate that cognitive impairments as a consequence of sleep deprivation appear to be most severe with learning and memory processes that require the hippocampus, which suggests that this brain region is particularly sensitive to the consequences of sleep loss. Moreover, recent studies in laboratory rodents indicate that sleep deprivation impairs hippocampal neuronal plasticity and memory processes by attenuating intracellular cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling. Attenuated cAMP-PKA signaling can lead to a reduced activity of the transcription factor cAMP response element binding protein (CREB) and ultimately affect the expression of genes and proteins involved in neuronal plasticity and memory formation. Pharmacogenetic experiments in mice show that memory deficits following sleep deprivation can be prevented by specifically boosting cAMP signaling in excitatory neurons of the

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hippocampus. Given the high incidence of sleep disturbance and sleep restriction in our 24/7 society, understanding the consequences of sleep loss and unraveling the underlying molecular mechanisms is of great importance.

Keywords Sleep deprivation · Sleep disturbance · Hippocampus · Learning · Memory · Long-term potentiation · LTP · cAMP · PDE · CREB · mTOR

Contents

1 Introduction

In the late 1800s, Herman Ebbinghaus published the seminal work "*Über das Gedachtnis. Untersuchungen zur experimentellen Psychologie*" in which he proposed that memories decay over time (Ebbinghaus 1885). In that same time period, Philip Ballard taught thousands of children lines from "Rhyme of the Ancient Mariner" by English poet Samuel Taylor Coleridge and showed that memories can actually get stronger with the passage of time (Ballard 1913). Even earlier in 1801, the British psychologist David Hartley already proposed that associative memories could be modulated by dreaming (Hartley 1801). His hypothesis was eventually tested a century later by Jenkins and Dallenbach (1924) who showed that sleep promoted memory storage in human subjects. Since then, numerous studies in a variety of species have supported the observation that sleep is beneficial for memory and in recent decades, sophisticated techniques have been used to elucidate the signaling processes and molecular mechanisms that contribute to memory and are modulated by sleep and sleep loss. In this review, we will first discuss the benefit of sleep on different forms and stages of memory with emphasis

on memory consolidation. Afterward, we will briefly discuss recent insights in the molecular mechanisms that are critical for these processes and are bidirectionally regulated by sleep and sleep loss. This review largely focuses on animal models, which have been the basis of much of our current knowledge of the molecular mechanisms underlying the relationship between sleep and memory.

2 Three Stages of Memory

Memory consists of at least three distinct stages (Abel and Lattal 2001; Fig. 1). The first stage is the memory acquisition or encoding stage that starts as soon as animals are subjected to training in the behavioral paradigm. The second stage entails the consolidation phase during which a labile, short-term memory is transformed to a stable long-term memory. The consolidation phase starts after the task has ended and lasts for at least several hours. The final stage is memory retrieval, which can happen up to years after the memory has been formed and is initiated by re-exposing an animal to the task or training context. To probe the mechanism underlying each of these stages, a variety of different approaches have been used, including transgenic and knockout mice, lesions of specific brain regions, and pharmacological manipulations of specific signaling systems. To address the role of sleep in memory processes, timed sleep deprivation for varying durations has been applied at different stages to assess the effects on behavioral performance and to collect brain material for assessment of cellular and molecular changes underlying the changes in memory. Recent advances in molecular biology have allowed for a combination of different techniques (e.g., pharmacogenetics) to manipulate specific signaling pathways in a brain region and cell-type-specific fashion (for example see, Havekes et al. 2014). These techniques do not only help to elucidate the molecular mechanisms underlying memory, but they also allow researchers to elucidate the role of sleep in the specific memory processes. Much of this work has focused on sleep and memory consolidation, although data are available that support a role for sleep in the initial memory encoding as well (Fig. 2). There is a general paucity of data on sleep, sleep deprivation, and memory retrieval, and this issue will therefore not be discussed in great detail.

3 Methods of Sleep Deprivation

To study the contribution of sleep in different stages of memory, research laboratories use a variety of methods to keep animals awake. To keep animals awake for a few hours, some laboratories use the gentle stimulation method, which is aimed at keeping animals awake with as little disturbance as possible, that is, by tapping on the cage, gently shaking of the cage, or, if necessary, by disturbing the nesting

material (van der Borght et al. 2006; Vecsey et al. 2009; Hagewoud et al. 2010a, b, c, 2011; Havekes et al. 2014; Prince et al. 2014). Many laboratories use variations of this procedure, and collectively, these procedures are commonly referred to as the gentle handling method. Often, animals are kept awake by introducing novel objects and new nesting material, or by actually taking them out of their cage, handling them, and exposing them to novel environments (Cirelli and Tononi 2000; Cirelli et al. 2006; Kopp et al. 2006; Vyazovskiy et al. 2008; Longordo et al. 2009a, b). It should be noted that cross comparison of studies using these different sleep deprivation procedures can be challenging as they may differentially impact brain plasticity. Indeed, exposure to novel objects and novel environments itself could lead to enhanced synaptic plasticity and these changes may be different from or even opposite to the effects of sleep loss (for detailed review, see Havekes et al. 2012).

Another commonly used procedure to keep animals awake is subjecting them to forced locomotion by means of motorized slowly rotating drums, treadmills, or revolving floors (Tobler and Jaggi 1987; Roman et al. 2005; Sportiche et al. 2010; Leenaars et al. 2011; Novati et al. 2011). An obvious advantage of this automated procedure is that it does not require constant involvement of the experimenters and can therefore be applied for prolonged periods of time. Novelty of the sleep deprivation apparatus can be reduced by habituating the animals prior to the experiment. In addition, control animals can be held in same setup without actually letting the wheels, treadmills, or floors move or letting them move at a higher speed for shorter intervals so that these control animals cover the same distance in a shorter time frame and thus have sufficient time for sleep (e.g., Novati et al. 2011; Roman et al. 2005). Such manipulations are also ideal to assess the impact of chronic partial sleep deprivation as it often occurs in society. Animals are deprived of sleep for only a certain amount of hours on a daily basis, but just do not get enough sleep to fully recover (Roman et al. 2005).

A refinement of the various forced locomotion procedures includes the simultaneous recording of brain activity (electroencephalogram, EEG) and muscle activity (electromyogram, EMG), which can be used to initiate and restrict apparatus movement to only those times when EEG and EMG indicate sleep onset (Bergmann et al. 1989; Guzman-Marin et al. 2008). This approach can also be used for manipulation of specific sleep stages such as rapid eye movement (REM) sleep by initiating apparatus movement when the computer recognizes the EEG and EMG characteristics of this sleep stage (Guzman-Marin et al. 2008). This refined automated method has the advantage that it minimizes the amount of forced activity, but requires surgery for implantation of EEG/EMG electrodes and also requires hardware and software for recording and online analysis of the EEG and EMG signals.

The specific role of REM sleep in brain function and memory processes can also be studied by means of the older but still frequently used platform-over-water or flowerpot method (Mendelson et al. 1974). The essence of this method is that animals are placed on a small platform, often an inverted flowerpot, surrounded by water. The platform or flowerpot is just large enough for animals to lie down and have most of their non-REM sleep or slow-wave sleep, because they maintain a

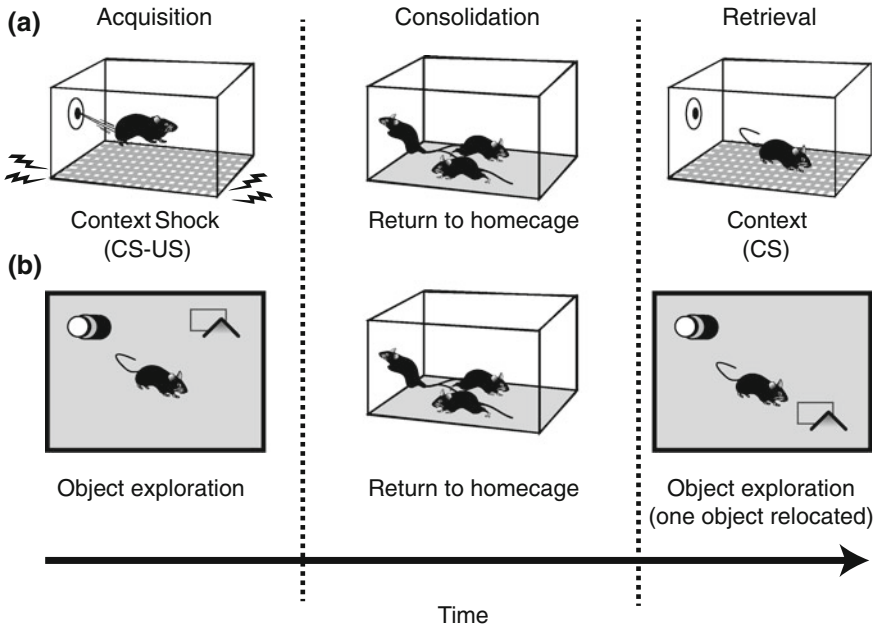

Fig. 1 Three distinct stages of memory as illustrated by two commonly used learning paradigms. Panel **a** shows the three different stages of memory for contextual fear conditioning. Rodents are allowed to explore a training context and are subjected to a mild electrical shock. During this acquisition stage, a memory for context–shock association is encoded. After training, the animals are returned to the home cage and the consolidation stage starts in which the newly formed memory is consolidated into a long-lasting memory. The memory for the context–shock association is retrieved by re-exposing the animals to the training context, and memory is assessed by measuring freezing behavior (the lack of locomotor activity except for respiratory behavior). Fear conditioning often results in a robust memory for the context–shock association after a single shock presentation, which allows these stages of memory to be isolated in time. **b** In case of object-location memories, the first stage entails the exploration of a context with two or three distinct objects in specific locations. At the end of the training, the animals are returned to the home cage and the new memory for the object locations is consolidated into a stable long-term memory. The memory for the object locations is tested by re-exposing the animals to the training context but now with one object moved to a novel location. If the animal formed a proper memory for the original location of each object, it will notice that one object was moved and will spend more time exploring the relocated object relative to the non-relocated objects as rodents have the natural tendency to explore familiar object in novel locations

minimal amount of muscle tension, but upon entering REM sleep, the complete loss of muscle tone associated with this stage makes the animals' head dip into the water, which then wakes it up. The charm of this method is that it requires no sophisticated equipment and is therefore cheap and easy. However, it is often criticized for its various potential confounding factors such as the stress associated with movement restriction or the risk of falling into the water, which may affect physiology and behavior of the animals, but have little to do with the loss of REM

sleep. Systems of multiple, connected platforms are being used to reduce the movement restriction in the experimental animals (Coenen and van Luijtelaar 1985). Control animals are generally placed on larger platforms, which allow them to get most of their usual non-REM and REM sleep.

4 Sleep and Fear Memories

Fear conditioning, recently also referred to as threat detection, is a popular learning paradigm to study the encoding and consolidation of fear memories in rodents and serves as a model to elucidate the molecular underpinnings of negative emotional memories (Fig. 1a). Rodents are trained to associate a neutral stimulus such as a context or tone (referred to as the conditioned stimulus, CS) with an aversive stimulus, which most commonly is a mild electrical shock (referred to as the unconditioned stimulus, US). During contextual fear conditioning, the experimental room and test box in which the shock is delivered serve as the US, and this form of fear conditioning requires an intact hippocampus (LeDoux 2000; Maren 2001). Tone-cued fear conditioning is a modified version of the same task in which a tone serves as the CS that is played prior to and during the delivery of the mild electrical shock. The formation of a tone–shock association critically relies on the amygdala rather than the hippocampus (LeDoux 2000; Maren 2001). Memory is most often tested about 1 or 24 h after the conditioning procedure, depending on whether one wants to assess short-term or long-term fear memory formation. Behavioral freezing levels are measured, that is, the complete lack of locomotor activity with the exception of respiratory movement, and higher levels of freezing are used as an indication of a stronger CS-US association. The elegance of this one-trail learning paradigm is that it allows researchers to dissect the role of sleep in the encoding and consolidation of fear memories by manipulating sleep prior to training or directly after training, respectively, as sleep deprivation post-training will only affect memory consolidation.

Several studies in laboratory rats have shown that extended (REM) sleep deprivation for 1–4 days prior to acquisition impairs subsequent encoding and/or formation of contextual fear memories (McDermott et al. 2003; Ruskin et al. 2004; Chen et al. 2006; Tiba et al. 2008; Fernandes-Santos et al. 2012). In one study, prolonged sleep deprivation had no effect on the acquisition of tone-cued fear conditioning (Ruskin et al. 2006). An important implication of this latter finding is that, apparently, sleep deprivation does not have a generalized effect on memory processes but impacts more strongly on specific pathways and brain regions. It seems that encoding of fear memories is more easily impaired by sleep deprivation when it involves the hippocampus, as is the case with contextual fear conditioning, but not so much when it only depends on the amygdala, as is the case with tone-cued fear conditioning. Another implication of these results is that the sleep deprivation-induced memory impairments are not likely a non-specific consequence of fatigue and decreased alertness since the animals were still able to process and use tone-cued

information to encode memories. In fact, even with reduced volume cues (down to approximately 10 dB above background noise), 24 h of sleep deprivation failed to impact the encoding of tone-cued fear memories (Ruskin and LaHoste 2009).

In some of the work described in the previous paragraph, rats were subjected to prolonged sleep deprivation by means of the flowerpot or platform-over-water method. To assess whether the impairments in contextual fear conditioning were a consequence of stress hormones, one study included groups with surgically removed adrenals, the main source of glucocorticoid stress hormones. Adrenalectomy in these animals did not prevent the sleep deprivation-induced memory impairments suggesting that elevated corticosterone release as a result of sleep deprivation was not the main cause of the cognitive deficits associated with loss of sleep (Tiba et al. 2008).

With respect to the role of sleep in the consolidation stage, work by different laboratories has clearly shown that depriving animals of sleep for 5–6 h directly after training in the contextual version of the task impairs the formation of contextual fear memories (Graves et al. 2003; Vecsey et al. 2009; Hagewoud et al. 2010a, 2011). Rats or mice were transferred to the shock box, exposed to a mild foot shock, and then returned to their home cage where they were sleep deprived for 5–6 h. The next day, generally 24 h after the conditioning, animals were re-exposed to the shock box to test their memory. During the re-exposure, the animals that had been sleep deprived displayed a significantly diminished freezing response as compared to the control animals that had not been sleep deprived. This finding suggests that loss of sleep during the first few hours after the training negatively impacted memory consolidation. Importantly, in between the sleep deprivation and the re-exposure to the shock box, all animals had sufficient time to sleep and recover, so the behavioral deficits during the re-exposure test could not be explained by fatigue. Also, the impairment was not observed when the sleep deprivation window was delayed for 5 h (i.e., sleep deprivation from 5 to 10 h after training rather than 0–5 h after training), which confirms that the effects of immediate sleep deprivation upon memory next day was not a consequence of remaining fatigue (Graves et al. 2003). The latter finding further suggests that there is a specific time window after acquisition during which memory formation is supported by sleep and can be disrupted by sleep deprivation (Graves et al. 2003).

In contrast to hippocampus-dependent contextual fear memories, the consolidation of tone-cued fear memories does not require the hippocampus but, rather, depends on the amygdala. This form of conditioning is not disrupted by a brief period of sleep deprivation following training (Graves et al. 2003). In agreement with the findings on sleep deprivation prior to memory encoding, this observation suggests that memory consolidation is particularly susceptible to sleep deprivation or sleep disruption when it involves the hippocampus and less so when it depends mostly on the amygdala (Graves et al. 2003).

The interference theory of forgetting implies that processing newer information interferes with storing and remembering previously learned information (retroactive interference) (Robertson 2012). The cited studies on brief sleep deprivation and

contextual fear conditioning kept animals awake by means of the gentle stimulation or gentle handling method. It is a debate in the field of sleep research whether the reported memory deficits are caused by the stimulation the animals receive and the interference that may cause or by the lack of sleep per se. Recent work by Hagewoud and colleagues addressed this topic. The authors first conducted a contextual fear conditioning experiment during the light phase (i.e., subjective night) as described above and recorded the amount of stimulation that was necessary to keep animals awake for the first 6 h directly after training (Hagewoud et al. 2010a). Next, the authors repeated the fear conditioning experiment during the dark phase (i.e., subjective day) and applied the exact same amount of stimulation over 6 h that was required to keep animals awake for 6 h during the light phase regardless of whether the animal were already spontaneously awake or trying to sleep. This amount of stimulation when applied during the dark phase did not impair memory consolidation. This important finding indicates that the sleep deprivation-induced fear memory deficits observed when training and sleep deprivation was conducted in the light phase were not a consequence of the method used to deprive animals of sleep, but a result of the actual loss of sleep. In contrast to 6 h of sleep deprivation during the dark phase, 12 h of sleep deprivation in the dark phase *did* hamper the long-term memory formation of contextual fear. Because sleep is more spread out across the dark phase, the authors concluded that the amount of sleep in addition to sleep during a specific time window after training is another important factor for memory consolidation (Hagewoud et al. 2010a).

5 Sleep, Object-Place Memories, and Object-Identity Memories

Object memory tasks are based on the rodent's natural tendency to explore spatial novelty (Fig. 1b). Generally, the animals are transferred to a test room and allowed to freely explore a context equipped with a number of unique objects during an initial training session (acquisition phase). After a certain period of time, which can range from hours to days, the animals are returned to the test box (test phase) in which one object has been moved to a new location in the box or has been replaced by a new one. The animals then have to discriminate familiar from novel objects (object-identity recognition task) or determine which familiar object has moved to a novel location (object-location memory task). Their ability to discriminate the familiar objects or locations from novel objects or locations is reflected in their preferential exploration of the novel objects and location. As with fear conditioning, the elegance of these behavioral assays lies in the fact that they are brief, one-session learning tasks allowing for easy manipulation of sleep either prior or after training. In addition, these paradigms have great translational potential because versions of the same task can be used in both animal models and humans.

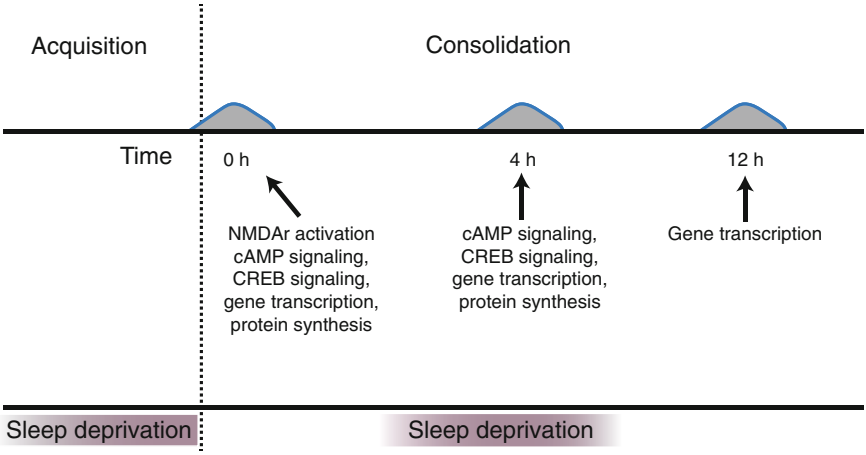

Fig. 2 Sleep deprivation can affect different phases of memory. Sleep deprivation prior to learning can impair memory acquisition, and sleep deprivation after training can have a negative effect on memory consolidation. During the consolidation phase, there are multiple time windows in which specific molecular processes contribute to the formation of a stable long-term memory. During the first window, directly after training at the beginning of memory consolidation, these include NMDA receptor activation, cAMP signaling, CREB-mediated gene transcription, and the synthesis of novel proteins. During the second period, approximately 4 h after training, there is a second wave of cAMP signaling, CREB-mediated gene transcription, and protein synthesis. Gene transcription 12 h after training also contributes to the memory consolidation process. In case of the object-location memory task, sleep deprivation specifically impacts memory consolidation during a 3 h window starting 1 h after training (i.e., from 1 to 4 h after training)

While to our knowledge, there have been no studies on sleep deprivation prior to the acquisition phase in the object-identity or object-location memory paradigms, various studies have assessed the effects of sleep deprivation immediately following training. The object-location memory task critically depends on the hippocampus (Winters et al. 2004; Oliveira et al. 2010), and 5–6 h of sleep deprivation directly after training impairs the memory consolidation for object location. When mice are re-tested in the task 24 h after conditioning, they fail to discriminate the relocated from non-relocated objects (Florian et al. 2011; Havekes et al. 2014). A recent study further refined the window during which sleep deprivation impacted memory consolidation in this task by showing that 3 h of sleep deprivation significantly impaired memory formation when deprivation began 1 h after training. In contrast, 3 h of deprivation beginning immediately post-training did not impair spatial memory (Prince et al. 2014; also, see Fig. 2).

In addition to object-location memories, a number of studies have indicated that 5–6 h of brief sleep deprivation directly after acquisition using the mild stimulation method significantly reduced the preferential exploration of a novel object relative to familiar objects the next day. These findings indicate that the consolidation of object-identity memories just like the consolidation of object-location memories is negatively impacted by sleep deprivation (Palchykova et al. 2006; Halassa et al.

2009). Using an optogenetic approach to wake up mice by activating orexin/hypocretin neurons, the laboratory of de Lecea recently found that the consolidation of memories for object identity is attenuated by sleep fragmentation during the first 4 h after training (Rolls et al. 2011). When the average duration of sleep episodes was maintained at around 70 % of normal, the memory for the object identity was unaffected. An important implication of this study is that in addition to total sleep deprivation even subtler manipulations such as mild sleep fragmentation may already lead to memory impairments. Secondly, because the optogenetic method of sleep disruption does not require handling or physical stimulation of the animals, it strongly supports the view that the memory deficits are a consequence of an impairment or loss of sleep per se rather than the stimulation that is provided to keep the animals awake.

There is some controversy regarding the involvement of the hippocampus in the formation of memories for object identities. Some studies indicate that the perirhinal cortex rather than the hippocampus is critical for the consolidation of object identities (Brown and Aggleton 2001; Winters and Bussey 2005; Oliveira et al. 2010), while others suggest that the hippocampus is critical for this process (Cohen et al. 2013). Recent work addressed this issue and revealed that when the number of objects in the task was increased (thus making the task more difficult) it became more and more dependent on the hippocampus (Sannino et al. 2012). Because sleep deprivation also impairs memory consolidation of object identity using a simple version of the task that does not require the hippocampus, other regions such as the perirhinal cortex may also be susceptible to sleep loss (Halassa et al. 2009; Oliveira et al. 2010).

6 Sleep, Spatial Memories, and Behavioral Strategies

The formation of spatial memories, just like contextual fear and object-location memories, requires proper hippocampal function. To study spatial learning in rodents, a variety of behavioral paradigms have been developed. One of the most frequently used assays to study spatial and non-spatial learning and memory processes in rodents is the Morris water maze (Morris et al. 1982). The essence of this task is that animals are placed in a large pool of opaque water and learn that they can escape from the water by finding a submerged platform. In the hippocampus-dependent spatial version, the animals have to learn to locate the platform on the basis of spatial cues that are present around the pool. The task is made hippocampus-independent by a single visual cue such as a flag directly marking the specific location of the platform. In contrast to the fear conditioning and object tasks, the water maze is a more complex, multi-trial learning task and often animals are subjected to multiple training sessions on successive days.

Animals that were deprived of REM sleep using the flowerpot method for 12 h directly after training had greater difficulty learning platform location reflected in a longer latency time to find the platform in the water maze. Delaying the REM sleep

deprivation period for 12 h did not affect memory consolidation suggesting that the memory deficit in the first experiment was due to hampered memory consolidation rather than fatigue as a result of sleep loss (Smith and Rose 1996). In line with this, even as little as 4 h of REM sleep deprivation immediately following training was sufficient to impair this form of memory (Smith and Rose 1996).

The observation that REM sleep is critical for the spatial learning in the Morris water maze has been confirmed by some laboratories (Youngblood et al. 1997; Guan et al. 2004; Yang et al. 2008; Li et al. 2009), but not by some others (Wang et al. 2009; Walsh et al. 2011). The apparent inconsistent findings on the consequences of sleep deprivation in the water maze may be explained by the fact that animals while undergoing training can adopt alternative behavioral learning strategies that are not necessarily dependent on the hippocampus (Bjorness et al. 2005; Hairston et al. 2005). Instead of locating the platform on the basis of the spatial cues in the testing room, animals may confer to using other strategies that do not rely on those cues. In other words, even when sleep deprivation presumably impaired hippocampal function, the animals were still able to learn the location of the platform using more random behavioral strategies based on different brain mechanisms. An important implication of these findings is that effects of sleep deprivation in the brain, even when they are there, may not always be directly evident at the behavioral or cognitive level.

The observation that loss of sleep can lead to the use of alternative behavioral strategies has also been reported by others using different spatial learning paradigms, including the 8-arm radial maze task (Bjorness et al. 2005) and the y-maze or T-maze task (Hagewoud et al. 2010b). Using a two-arm reference task in which animals have to learn and remember the location of a food reward, Hagewoud and colleagues (2010b) showed that sleep deprivation directly following each training session did not directly affect the rate at which mice learned which arm was baited. However, sleep deprivation did induce a shift in the behavioral strategy used to locate the food reward. Whereas a majority of control animals used a spatial strategy based on cues in the room to locate the baited arm, the sleep-deprived mice learned to make a specific turning response, independent of spatial cues. The latter was demonstrated at the end of the training phase, when all animals had successfully learned to locate the baited arm, by basically turning the T-maze 180° and subjecting the animals to a probe trial starting from the opposite spatial location. Despite the altered spatial location of the start arm, the majority of control animals went to the original and correct spatial location for the food reward. Instead, the sleep-deprived animals made the same turn as they had learned to do and therefore went into the opposite arm. Thus, instead of a spatial strategy, the sleep-deprived mice used a so-called response-based strategy, which is known to be dependent on the striatum rather than the hippocampus (Hagewoud et al. 2010b). By doing so, the mice presumably compensated for a sleep deprivation-induced hippocampal deficit by recruiting brain regions apparently less sensitive to sleep loss. Indeed, analysis of brain material showed that the shift in behavioral strategy was paralleled by a shift in regional brain activation from hippocampus to striatum (Hagewoud et al.

2010b). The observation that sleep deprivation may facilitate of striatum-dependent learning has also been suggested by other studies (Watts et al. 2012).

Importantly, while sleep-deprived mice in these maze studies by Hagewoud and colleagues performed well during the initial training, their performance was attenuated when they had to adapt their memory in a subsequent reversal-learning paradigm. In this reversal-learning task, the mice had to learn that the previously rewarded arm was no longer rewarded and that the previously non-rewarded arm was now rewarded. The sleep-deprived mice required significantly more training sessions to adapt to this changed situation than the control mice (Hagewoud et al. 2010b). The authors explained this outcome by the well-known rigidity of the striatal memory system as compared to the more flexible hippocampal memory system used by the control animals (Hartley et al. 2003).

Together, these findings have two important implications. One, when the nature of the task allows this, the negative effects of sleep deprivation on hippocampal function and cognition may be temporarily compensated for through the recruitment of other brain regions and alternative learning strategies. Two, the use of such alternative learning mechanisms can result in reduced flexibility, which may still have negative consequences for performance later on, when changing conditions require adaptation of the previously formed memories. These observations in rodents parallel imaging work in humans showing shifts in activity of specific brain regions as a consequence of sleep deprivation (Orban et al. 2006; Rauchs et al. 2008).

7 Sleep Deprivation and Working Memory

Certain spatial learning paradigms have also been used to assess more specifically the effects of sleep deprivation on working memory. One task that is particularly well suited to address this question is the novel-arm recognition task in which rodents have to discriminate a novel arm from familiar ones that have been explored two minutes prior to the test, a form of working memory that also critically depends on the hippocampus, but not the prefrontal cortex (Etkin et al. 2006). Non-sleep-deprived mice preferentially explored the novel arm during the test session suggesting that they formed a short-term memory for those arms they already explored during training. In contrast, mice sleep deprived for 12 h prior to exposure to the task did not discriminate between familiar and novel arms and explored all arms to a similar level due to the lack of an accurate short-term memory for the previously explored arms. Mice that were deprived of sleep for 6 h showed an intermediate phenotype (Hagewoud et al. 2010c). The deficit in working memory was not a consequence of reduced motivation due to fatigue because the total number of arm entries was not affected by sleep loss. These findings are conform studies in humans that have indicated that a single night of sleep deprivation or even mild sleep disruption is sufficient to impair the memory encoding process that coincides with reduced hippocampal activity (Yoo et al. 2007; Van Der Werf et al. 2009).

8 Sleep Deprivation and the Molecular Machinery Underlying Memory Consolidation

The emerging picture from the behavioral studies in animals described in the previous paragraphs is that those cognitive processes that require the hippocampus benefit from sleep and are particularly sensitive to sleep loss. The true value of these animal models of course lies in the fact that they can be used for experimentation and detailed analysis of underlying cellular and molecular mechanisms that cannot be done in human subjects. In the next section, we will describe recent insights in the molecular signaling pathways critical for the consolidation of hippocampus-dependent long-term memories and discuss how sleep and sleep loss alters these processes (for an overview, see Fig. 3).

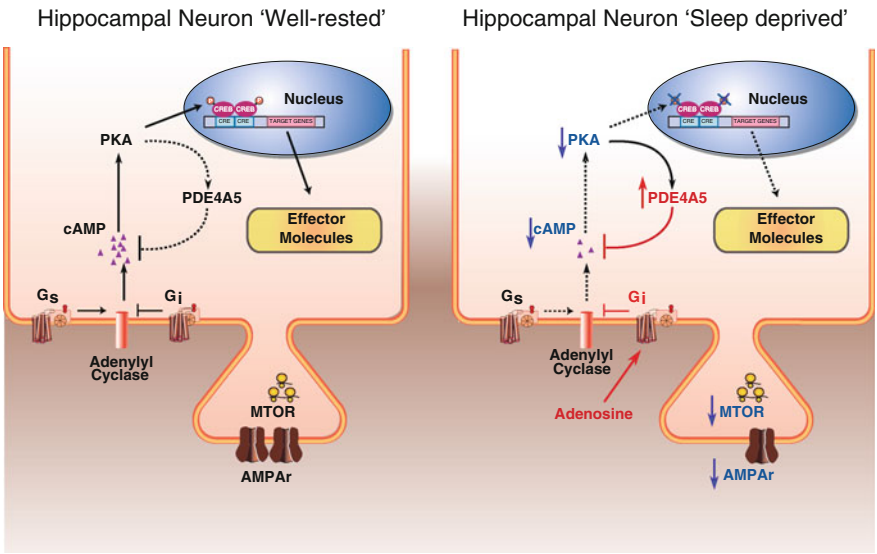

Fig. 3 The molecular impact of sleep deprivation on pathways critical for memory consolidation. A schematic overview of some of the hippocampal signaling pathways whose modulation by sleep deprivation may contribute to the effects of sleep deprivation on memory encoding and consolidation. *Left Panel* signaling pathways under normal well-rested conditions. *Right Panel* sleep deprivation has been reported to reduce cAMP signaling leading to reduced AMPA receptor phosphorylation and CREB-mediated gene transcription. Sleep loss also hampers translation initiation through the mTOR pathway. *Dashed black lines* and *blue arrows* pointing down indicate attenuation of the signaling pathway. *Red labels* and *lines* indicate an increase of the signaling pathway in the sleep deprived condition relative to the well-rested condition

8.1 Sleep Deprivation Attenuates cAMP Signaling

Time course analysis of the memory consolidation period revealed that not one, but two critical time periods exist during which hippocampal mRNA synthesis and protein synthesis critically contributes to fear motivated learning (Bourtchouladze et al. 1998; Igaz et al. 2002). One of the pathways that modulate transcriptional processes during these two periods is the cAMP signaling pathway with PKA being one of the major targets of cAMP. Indeed, the formation of long-term spatial and contextual fear memories is disrupted by forebrain-specific suppression of PKA function (Abel et al. 1997; Isiegas et al. 2006) and by infusion of the PKA inhibitor Rp-cAMP bilaterally into the hippocampus (Bourtchouladze et al. 1998). Importantly, Rp-cAMP disrupts long-term fear memory formation when it is injected either directly after training or 4 h post-training. Because injections of the PKA inhibitor at other time points after training did not lead to memory deficits, the authors concluded that PKA signaling in the hippocampus contributes to the memory consolidation process in the first few hours after training (Bourtchouladze et al. 1998). This finding is of particular interest in light of the studies discussed in previous sections showing that hippocampus-dependent memory formation is impaired by sleep deprivation during a similar time window (Graves et al. 2003; Hagewoud et al. 2010a, 2011; Florian et al. 2011; Havekes et al. 2014). In case of object-location memories, this time window has even been refined to 2–4 h after training (Prince et al. 2014). The similarity in time windows during which sleep deprivation and PKA-inhibition disturb memory consolidation raised the question whether hippocampal cAMP-PKA signaling is raised during sleep and suppressed by sleep deprivation. Several reports have provided evidence that this may indeed be the case. Recent work revealed that hippocampal cAMP signaling undergoes circadian oscillations with a peak around 4 h after the onset of the light period (Eckel-Mahan et al. 2008), which corresponds to the period in the light phase during which mice spent a significant time sleeping (Wimmer et al. 2013). Furthermore, hippocampal cAMP signaling is increased specifically during rapid eye movement sleep in the mouse hippocampus (Luo et al. 2013). Work by our laboratory revealed that loss of sleep has the inverse effect on the cAMP signaling pathway in the hippocampus; five hours of total sleep deprivation reduces cAMP levels in the hippocampus and impaired cAMP-dependent forms of synaptic plasticity that require PKA signaling (e.g., LTP induced by four spaced 100 Hz trains, thetaburst stimulation, or bath application with the adenylate cyclase activator forskolin) (Vecsey et al. 2009).

Subsequent studies showed that transiently increasing cAMP levels in hippocampal excitatory neurons during the course of sleep deprivation can prevent the memory deficits in some of the learning paradigms. Havekes and colleagues (2014) used a pharmacogenetic approach based on the expression of *Drosophila* octopamine receptors, which are normally not present in the mammalian brain, specifically

in the hippocampus of mice. Brain region-specific expression of the octopamine receptor was achieved by injecting a virus with the gene construct directly into the hippocampus. Expression of the receptor was restricted to excitatory neurons by using a CaMKIIα promoter fragment to drive transgene expression. Once the receptors were expressed, a simple intraperitoneal injection of the receptor ligand octopamine binding to the receptors was capable of activating adenylyl cyclases leading to a transient increase in cAMP. The authors then trained animals expressing the octopamine receptor or control animals expressing eGFP in the object-place recognition task and sleep deprived half of these groups for 5 h directly after training. All mice received two systemic injections with octopamine to boost cAMP production and prevent the previously reported decrease in cAMP levels during sleep deprivation. This transient upregulation of cAMP signaling selectively in hippocampal excitatory neurons was sufficient to prevent the memory impairments in the object-location memory task seen in sleep-deprived control animals. These studies thus provided evidence that local changes in cAMP in hippocampal neurons as a result of sleep deprivation during the consolidation window lead to memory deficits in a hippocampus-dependent task (Havekes et al. 2014).

8.2 Sleep Deprivation and Phosphodiesterase-Mediated Degradation of cAMP

The degradation of cAMP in the body is orchestrated by a large family of phosphodiesterases (PDEs) (Houslay and Adams 2003; Houslay 2009). It thus seemed a plausible explanation that the impairment of cAMP signaling during sleep deprivation might be caused by elevated PDE activity. Indeed, pharmacological inhibition of PDE activity prevented both the sleep deprivation-induced decrease in cAMP levels and reversed the deficit in forskolin-induced LTP (Vecsey et al. 2009). Moreover, systemic delivery of rolipram, a non-selective PDE4 inhibitor, to mice during 5 h of sleep deprivation directly after training prevented the memory impairments in the contextual fear memory task normally seen after sleep deprivation (Vecsey et al. 2009). These observations led to the conclusion that PDE4 signaling plays a central role in the cognitive deficits associated with sleep loss in case of hippocampus-dependent memory processes (Fig. 3).

The PDE4 family consists of four large subfamilies (PDE4A-D), and individual PDE isoforms are targeted to signalosomes located in specific intracellular compartments by their isoform-unique N-terminal regions (Houslay 2009; Houslay and Addams 2003). Sleep deprivation did not alter protein levels for PDE4B isoforms, PDE4D3, or PDE4D5 in the hippocampus. In contrast, a significant increase for PDE4A5 protein levels was observed (Vecsey et al. 2009). This observation of a specific increase in PDE4A5 suggests that sleep deprivation reduces cAMP in close proximity of PDE4A5 containing signalosomes. Because PDE isoforms differ in most cases only in their unique N-terminal domain, a major challenge will be to

develop pharmacological agents that specifically target PDE4A5 (or its human orthologue PDE4A4 Houslay 2009). Such reagents would indicate whether the cognitive impairments induced by sleep loss can be reversed by targeting this particular PDE4 isoform without affecting activity of other PDE4 isoforms.

In addition to the SD-induced and PDEA4-mediated degradation of cAMP, SD might also directly attenuate the production of cAMP by suppressing the activity of adenylyl cyclase. One upstream factor that might be responsible for such a decrease in adenylyl cyclase activity as a consequence of sleep loss is adenosine (Fig. 3). Adenosine itself is a product of cellular/neuronal energy consumption and results from the degradation of ATP (Basheer et al. 2004; Porkka-Heiskanen et al. 2002). It has been proposed that the extracellular release of adenosine may act as a neurochemical signal of sleep debt because in some brain regions, adenosine increases during wakefulness and declines during sleep (Huston et al. 1996; Porkka-Heiskanen et al. 1997). By acting on adenosine A1 receptors, adenosine inhibits neuronal activity and presumably protects the brain against over activity (Basheer et al. 2004; Porkka-Heiskanen et al. 2002). Yet, under conditions of sleep deprivation, adenosine may also inhibit the cAMP pathway and thereby attenuate neuronal plasticity and memory formation. Importantly, there is some indication that adenosine antagonists such as caffeine can indeed prevent SD-induced impairments in synaptic plasticity and cognitive function (Alhaider et al. 2010, 2011).

8.3 Sleep Deprivation and Downstream Targets of cAMP Signaling

While the work described above provides evidence that hippocampal cAMP-PKA signaling may be one of the critical pathways affected by sleep deprivation and playing a role in the cognitive deficits associated with loss of sleep, it remains to be determined how alterations in cAMP content ultimately lead to synaptic plasticity impairments and memory deficits.

One possibility is that a SD-induced suppression of cAMP-PKA signaling directly affects the phosphorylation and thereby expression of glutamate receptor subunits at the cell membrane, which partly determines neuronal excitability and the strength of neuronal connections. For example, 6–12 h of SD by gentle stimulation was found to reduce hippocampal glutamate AMPA receptor phosphorylation at the S845 site of the GluA1 subunit (Hagewoud et al. 2010c). Because phosphorylation of the S845 site is crucial for incorporation of the receptors into the membrane (Lee et al. 2000; Esteban et al. 2003), this finding suggests that brief SD may decrease membrane surface expression of AMPA receptors. However, attenuated AMPA receptor signaling has not been found in some other studies (McDermott et al. 2006; Vyazovskiy et al. 2008).

Alternatively, impaired cAMP-PKA signaling may result in reduced phosphorylation and activity of transcription factors such as CREB, which regulates the expression of a wide range of genes involved in synaptic plasticity and memory formation. Indeed, studies in rodents show that brief SD for only five–six hours can attenuate basal CREB phosphorylation in the hippocampus (Vecsey et al. 2009) and may also attenuate the increase in CREB phosphorylation normally associated with learning and memory processes (Alhaider et al. 2011; Hagewoud et al. 2011). Moreover, while brief SD up to 6 h is capable of reducing hippocampal phosphorylation and activity of CREB, prolonged sleep fragmentation for 48 h was even reported to reduce the overall levels of CREB protein (Guzmán-Marín et al. 2006).

In contrast, CREB phosphorylation in the amygdala is attenuated after long periods of REM sleep deprivation, but not by brief periods of total sleep deprivation (Vecsey et al. 2009; Pinho et al. 2013). The latter finding may explain why amygdala-dependent tone-cued fear conditioning is less susceptible to sleep loss than hippocampus-dependent contextual fear conditioning (Sect. 4, Graves et al. 2003). It thus seems that CREB function is altered by sleep and sleep loss in a brain region-specific fashion. Interestingly, a study discussed in Sect. 5 showed that mice subjected to SD shifted from a hippocampal learning strategy to a striatum-based learning strategy, and this shift in cognitive strategy was paralleled by a shift in CREB phosphorylation from the hippocampus to the dorsal striatum (Hagewoud et al. 2010b). Further studies are required to assess whether the changes in regional CREB phosphorylation are responsible for the differences in learning strategy or whether the shift in behavioral strategy causes the alterations in phosphorylated CREB expression.

Importantly, there is some data to suggest that the reported SD-induced attenuation of CREB activity may not only be a consequence of reduced cAMP-PKA signaling, but may also result in part from reduced activity of other kinase signaling pathways. Particularly, the extracellular signal-regulated kinase (ERK, also known as MAPK) is involved in the regulation of CREB (Davis et al. 2000; Kandel 2004) and is also a pivotal component for memory storage (Impey et al. 1999; Mazzucchelli and Brambilla 2000; Sweatt 2004). Six hours of total sleep deprivation as well as multiple days of REM sleep deprivation reduces hippocampal P44/P42 ERK phosphorylation (Guan et al. 2004; Ravassard et al. 2009; Park et al. 2012). Furthermore, P44/42 phosphorylation in the hippocampus just like cAMP signaling is upregulated specifically during REM sleep as compared to waking or NREM sleep (Luo et al. 2013).

8.4 Sleep Deprivation and Translational Processes

The data described in the previous section indicate that SD may have pronounced effects on gene expression and through that it may ultimately affect the synthesis of proteins involved in the consolidation of previously acquired information. Indeed, sleep increases mRNA levels of genes associated with protein synthesis and membrane trafficking (Cirelli et al. 2004; Mackiewicz et al. 2007) and deprivation of sleep down regulates expression of genes associated with RNA binding and

translational processing (Vecsey et al. 2012). A bioinformatic analysis of changes in gene expression in the mouse hippocampus after brief 5-h SD revealed that a prominent effect of SD was a down regulation in translational activity, potentially mediated by the mammalian target of rapamycin (mTOR), a key regulator of protein synthesis (Vecsey et al. 2012). Consistent with this analysis was the finding the SD reduced mTOR levels and that these levels returned to normal after 2.5 h of recovery sleep levels (Vecsey et al. 2012). Moreover, work by the laboratory of Marcos Frank extended this finding by demonstrating that sleep-dependent consolidation of plasticity in the visual cortex of cats depends on mTOR-dependent pathways and that sleep is associated with increased phosphorylation of protein synthesis regulators such as eEF2 and 4E-BP1 (Seibt et al. 2012). Together, these findings suggest that sleep loss negatively impacts protein signaling complexes important for translation initiation and thereby attenuates the synthesis of proteins that are required for memory formation.

9 Conclusions and Future Perspectives

The current view in the field of sleep research is that sleep is beneficial for cognitive function, while loss of sleep generally perturbs nuclear and synaptic processes critical for learning and memory (Abel et al. 2013; Havekes et al. 2012). Several lines of evidence indicate that this is the case in particular for those memories that depend on the hippocampus. At the molecular level within the hippocampus, recent studies have implicated an attenuation of cAMP-PKA signaling in SD-induced memory deficits. Such an attenuated cAMP-PKA signaling may directly affect glutamate receptor function and neuronal excitability but it may also affect CREB-mediated gene expression, translational processes, and synthesis of proteins involved in the formation and consolidation of memories.

While the development of new molecular techniques have led to novel insights into the brain regions and molecular pathways involved in SD-induced memory impairments, many important unresolved issues remain. For example, one important unanswered question is why the hippocampus appears to be more susceptible to sleep loss than other areas of the brain that are involved in memory processes as well, such as the amygdala or the striatum. At the molecular level, much has to be learned about the upstream mechanisms that cause the suppression of cAMP signaling during SD, particularly, the processes that may lead to a decrease in adenylyl cyclase-mediated production of cAMP, or processes that may lead to an increase in PDE-mediated breakdown of cAMP. Also, the downstream targets from cAMP that ultimately lead to impaired memory formation under condition of SD are only partly understood. While transcriptional and translational processes are clearly implicated in the negative effects of SD, it remains to be established what the critical proteins or protein complexes are that ultimately make up a memory trace and that are disturbed by sleep loss.

Another topic that requires attention in future studies is the role of sleep in systems consolidation, that is, the transfer of recent memories from brain structures such as the hippocampus to cortical layers. Based on studies in humans, the general assumption is that such a transfer can happen rapidly, with just a night of sleep or even a nap (for detailed reviews see Dudai 2004; Frankland and Bontempi 2005). Work by Ribeiro and colleagues (2002) has suggested that in rats, sleep may contribute to the transfer of memories from one structure to another as well, but data are scarce and require confirmation. Importantly, other data in rodents suggest that memory transfer, if it occurs at all, may be much slower than in humans. In case of contextual fear conditioning, lesions of the hippocampus 1 day after training causes substantial memory deficits in rodents. Only when the lesions were applied much later (i.e., 1–3 months after training), loss of the hippocampus no longer impacted memory retrieval in the same task (reviewed in Anagnostaras et al. 2001). Because rodents just like humans sleep on a daily basis (albeit the transitions between sleep stages are much more frequent in rodents), it will be of importance to define the molecular bases of these discrepancies in systems consolidation.

Finally, while the work described in this chapter provides a solid framework for future studies to define how sleep loss perturbs brain function at the cellular and molecular level, it should be noted that most studies have focused on the impact of acute sleep deprivation on the critical parts of memory consolidation. However, it is of great importance to also assess the consequences of more chronically restricted or disrupted sleep, as it often occurs in our modern society. Does chronically insufficient sleep perhaps lead to more pronounced and persistent changes in hippocampal plasticity and function? Does it ultimately also affect brain regions that are now assumed to be less susceptible to sleep deprivation? Does it perhaps not only disturb the formation of new memories but also undermine the stability of existing memories? And could it be that chronically restricted or disrupted sleep ultimately contributes to cognitive disorders and aging-related cognitive decline?

References

Abel T, Lattal KM (2001) Molecular mechanisms of memory acquisition, consolidation and retrieval. Curr Opin Neurobiol 11:180–187

Abel T, Nguyen PV, Barad M, Deuel TA, Kandel ER, Bourtchouladze R (1997) Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell 88:615–626

Abel T, Havekes R, Saletin JM, Walker MP (2013) Sleep, plasticity and memory from molecules to whole-brain networks. Curr Biol 23:R774–R788

Alhaider IA, Aleisa AM, Tran TT, Alkadhi KA (2010) Caffeine prevents sleep loss-induced deficits in long-term potentiation and related signaling molecules in the dentate gyrus. Eur J Neurosci 31:1368–1376

Alhaider IA, Aleisa AM, Tran TT, Alkadhi KA (2011) Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. Mol Cell Neurosci 46:742–751

Anagnostaras SG, Gale GD, Fanselow MS (2001) Hippocampus and contextual fear conditioning: recent controversies and advances. Hippocampus 11:8–17

Ballard P (1913) Oblivescence and reminiscence. Br J Psychol Monograph Suppl 1:1–82
Basheer R, Strecker RE, Thakkar MM, McCarley RW (2004) Adenosine and sleep-wake regulation. Prog Neurobiol 73:379–396
Bergmann BM, Kushida CA, Everson CA, Gilliland MA, Obermeyer W, Rechtschaffen A (1989) Sleep deprivation in the rat: II. Methodology. Sleep 12:5–12
Bjorness TE, Riley BT, Tysor MK, Poe GR (2005) REM restriction persistently alters strategy used to solve a spatial task. Learn Mem 12:352–359
Bourtchouladze R, Abel T, Berman N, Gordon R, Lapidus K, Kandel ER (1998) Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. Learn Mem 5:365–374
Brown MW, Aggleton JP (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2:51–61
Chen C, Hardy M, Zhang J, LaHoste GJ, Bazan NG (2006) Altered NMDA receptor trafficking contributes to sleep deprivation-induced hippocampal synaptic and cognitive impairments. Biochem Biophys Res Commun 340:435–440
Cirelli C, Tononi G (2000) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. J Neurosci 20:9187–9194
Cirelli C, Gutierrez CM, Tononi G (2004) Extensive and divergent effects of sleep and wakefulness on brain gene expression. Neuron 41:35–43
Cirelli C, Faraguna U, Tononi G (2006) Changes in brain gene expression after long-term sleep deprivation. J Neurochem 98:1632–1645
Coenen AM, van Luijtelaar EL (1985) Stress induced by three procedures of deprivation of paradoxical sleep. Physiol Behav 35:501–504
Cohen SJ, Munchow AH, Rios LM, Zhang G, Asgeirsdottir HN, Stackman RW Jr (2013) The rodent hippocampus is essential for nonspatial object memory. Curr Biol 23:1685–1690
Davis S, Vanhoutte P, Pages C, Caboche J, Laroche S (2000) The MAPK/ERK cascade targets both Elk-1 and cAMP response element-binding protein to control long-term potentiation-dependent gene expression in the dentate gyrus in vivo. J Neurosci 20:4563–4572
Dudai Y (2004) The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 55:51–86
Ebbinghaus H (1885) Über das Gedachtnis. Untersuchungen zur experimentellen Psychologie. Duncker & Humblot, Leipzig
Eckel-Mahan KL, Phan T, Han S, Wang H, Chan GC, Scheiner ZS, Storm DR (2008) Circadian oscillation of hippocampal MAPK activity and cAmp: implications for memory persistence. Nat Neurosci 11:1074–1082
Esteban JA, Shi S, Wilson C, Nuriya M, Huganir RL, Malinow R (2003) PKA phosphorylation of AMPA receptor subunits controls synaptic trafficking underlying plasticity. Nat Neurosci 6:136–143
Etkin A, Alarcon JM, Weisberg SP, Touzani K, Huang YY, Nordheim A, Kandel ER (2006) A role in learning for SRF: deletion in the adult forebrain disrupts LTD and the formation of an immediate memory of a novel context. Neuron 50:127–143
Fernandes-Santos L, Patti CL, Zanin KA, Fernandes HA, Tufik S, Andersen ML, Frussa-Filho R (2012) Sleep deprivation impairs emotional memory retrieval in mice: influence of sex. Prog Neuropsychopharmacol Biol Psychiatry 38:216–222
Florian C, Vecsey CG, Halassa MM, Haydon PG, Abel T (2011) Astrocyte-derived adenosine and A1 receptor activity contribute to sleep loss-induced deficits in hippocampal synaptic plasticity and memory in mice. J Neurosci 31:6956–6962
Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6:119–130
Graves LA, Heller EA, Pack AI, Abel T (2003) Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. Learn Mem 10:168–176
Guan Z, Peng X, Fang J (2004) Sleep deprivation impairs spatial memory and decreases extracellular signal-regulated kinase phosphorylation in the hippocampus. Brain Res 1018:38–47

Guzman-Marin R, Suntsova N, Bashir T, Nienhuis R, Szymusiak R, McGinty D (2008) Rapid eye movement sleep deprivation contributes to reduction of neurogenesis in the hippocampal dentate gyrus of the adult rat. Sleep 31:167–175

Guzmán-Marín R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol 575:807–819

Hagewoud R, Whitcomb SN, Heeringa AN, Havekes R, Koolhaas JM, Meerlo P (2010a) A time for learning and a time for sleep: the effect of sleep deprivation on contextual fear conditioning at different times of the day. Sleep 33:1315–1322

Hagewoud R, Havekes R, Tiba PA, Novati A, Hogenelst K, Weinreder P, Van der Zee EA, Meerlo P (2010b) Coping with sleep deprivation: shifts in regional brain activity and learning strategy. Sleep 33:1465–1473

Hagewoud R, Havekes R, Novati A, Keijser JN, Van de Zee EA, Meerlo P (2010c) Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. J Sleep Res 19:280–288

Hagewoud R, Bultsma LJ, Barf RP, Koolhaas JM, Meerlo P (2011) Sleep deprivation impairs contextual fear conditioning and attenuates subsequent behavioural, endocrine and neuronal responses. J Sleep Res 20:259–266

Hairston IS, Little MT, Scanlon MD, Barakat MT, Palmer TD, Sapolsky RM, Heller HC (2005) Sleep restriction suppresses neurogenesis induced by hippocampus-dependent learning. J Neurophysiol 94:4224–4233

Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG (2009) Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61:213–219

Hartley D (1801) Observations on man, his frame, his deity, and his expectations. Scholars Facsimile & Reprint, Gainesville

Hartley T, Maguire EA, Spiers HJ, Burgess N (2003) The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. Neuron 37:877–888

Havekes R, Vecsey CG, Abel T (2012) The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. Cell Signal 24:1251–1260

Havekes R, Bruinenberg VM, Tudor JC, Ferri SL, Baumann A, Meerlo P, Abel T (2014) Transiently Increasing cAMP levels selectively in hippocampal excitatory neurons during sleep deprivation prevents memory deficits caused by sleep loss. J Neurosci 34:15715–15721

Houslay MD (2009) Underpinning compartmentalised cAMP signalling through targeted cAMP breakdown. Trends Biochem Sci 35:91–100

Houslay MD, Adams DR (2003) PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. Biochem J 370:1–18

Huston JP, Haas HL, Boix F, Pfister M, Decking U, Schrader J, Schwarting RK (1996) Extracellular adenosine levels in neostriatum and hippocampus during rest and activity periods of rats. Neuroscience 73:99–107

Igaz LM, Vianna MR, Medina JH, Izquierdo I (2002) Two time periods of hippocampal mRNA synthesis are required for memory consolidation of fear-motivated learning. J Neurosci 22:6781–6789

Impey S, Obrietan K, Storm DR (1999) Making new connections: role of ERK/MAP kinase signaling in neuronal plasticity. Neuron 23:11–14

Isiegas C, Park A, Kandel ER, Abel T, Lattal KM (2006) Transgenic inhibition of neuronal protein kinase A activity facilitates fear extinction. J Neurosci 26:12700–12707

Jenkins JG, Dallenbach KM (1924) Obliviscence during sleep and waking. Am J Psychol 35:605–612

Kandel ER (2004) The molecular biology of memory storage: a dialog between genes and synapses. Biosci Rep 24:475–522

Kopp C, Longordo F, Nicholson JR, Luthi A (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. J Neurosci 26:12456–12465

LeDoux JE (2000) Emotion circuits in the brain. Ann Rev Neurosci 23:155–184

Lee HK, Barbarosie M, Kameyama K, Bear MF, Huganir RL (2000) Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. Nature 405:955–959

Leenaars CH, Dematteis M, Joosten RN, Eggels L, Sandberg H, Schirris M, Feenstra MG, Van Someren EJ (2011) A new automated method for rat sleep deprivation with minimal confounding effects on corticosterone and locomotor activity. J Neurosci Methods 196:107–117

Li S, Tian Y, Ding Y, Jin X, Yan C, Shen X (2009) The effects of rapid eye movement sleep deprivation and recovery on spatial reference memory of young rats. Learn Behav 37:246–253

Longordo F, Kopp C, Luthi A (2009a) Consequences of sleep deprivation on neurotransmitter receptor expression and function. Eur J Neurosci 29:1810–1819

Longordo F, Kopp C, Mishina M, Lujan R, Luthi A (2009b) NR2A at CA1 synapses is obligatory for the susceptibility of hippocampal plasticity to sleep loss. J Neurosci 29:9026–9041

Luo J, Phan TX, Yang Y, Garelick MG, Storm DR (2013) Increases in cAMP, MAPK activity, and CREB phosphorylation during REM sleep: implications for REM sleep and memory consolidation. J Neurosci 33:6460–6468

Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI (2007) Macromolecule biosynthesis: a key function of sleep. Physiol Genomics 31:441–457

Maren S (2001) Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci 24:897–931

Mazzucchelli C, Brambilla R (2000) Ras-related and MAPK signalling in neuronal plasticity and memory formation. Cell Mol Life Sci 57:604–611

McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003) Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 23:9687–9695

McDermott CM, Hardy MN, Bazan NG, Magee JC (2006) Sleep deprivation-induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. J Physiol 570:553–565

Mendelson WB, Guthrie RD, Frederick G, Wyatt RJ (1974) The flower pot technique of rapid eye movement (REM) sleep deprivation. Pharmacol Biochem Behav 2:5523–5556

Morris RG, Garrud P, Rawlins JN, O'Keefe J (1982) Place navigation impaired in rats with hippocampal lesions. Nature 297:681–683

Novati A, Hulshof HJ, Koolhaas JM, Lucassen PJ, Meerlo P (2011) Chronic sleep restriction causes a decrease in hippocampal volume in adolescent rats, which is not explained by changes in glucocorticoid levels or neurogenesis. Neuroscience 190:145–155

Oliveira AM, Hawk JD, Abel T, Havekes R (2010) Post-training reversible inactivation of the hippocampus enhances novel object recognition memory. Learn Mem 17:155–160

Orban P, Rauchs G, Balteau E, Degueldre C, Luxen A, Maquet P, Peigneux P (2006) Sleep after spatial learning promotes covert reorganization of brain activity. Proc Natl Acad Sci U S A 103:7124–7129

Palchykova S, Winsky-Sommerer R, Meerlo P, Durr R, Tobler I (2006) Sleep deprivation impairs object recognition in mice. Neurobiol Learn Mem 85:263–271

Park HJ, Kang WS, Paik JW, Kim JW (2012) Effect of valproic acid through regulation of NMDA receptor-ERK signaling in sleep deprivation rats. J Mol Neurosci 47:554–558

Pinho N, Moreira KM, Hipolide DC, Sinigaglia-Coimbra R, Ferreira TL, Nobrega JN, Tufik S, Oliveira MG (2013) Sleep deprivation alters phosphorylated CREB levels in the amygdala: relationship with performance in a fear conditioning task. Behav Brain Res 236:221–224

Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW (1997) Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science 276:1265–1268

Porkka-Heiskanen T, Alanko L, Kalinchuk A, Stenberg D (2002) Adenosine and sleep. Sleep Med Rev 6:321–332

Prince TM, Wimmer M, Choi J, Havekes R, Aton S, Abel T (2014) Sleep deprivation during a specific 3-hour time window post-training impairs hippocampal synaptic plasticity and memory. Neurobiol Learn Mem 109:122–130

Rauchs G, Orban P, Schmidt C, Albouy G, Balteau E, Degueldre C, Schnackers C, Sterpenich V, Tinguely G, Luxen A, Maquet P, Peigneux P (2008) Sleep modulates the neural substrates of both spatial and contextual memory consolidation. PLoS ONE 3:e2949

Ravassard P, Pachoud B, Comte JC, Mejia-Perez C, Scote-Blachon C, Gay N, Claustrat B, Touret M, Luppi PH, Salin PA (2009) Paradoxical (REM) sleep deprivation causes a large and rapidly reversible decrease in long-term potentiation, synaptic transmission, glutamate receptor protein levels, and ERK/MAPK activation in the dorsal hippocampus. Sleep 32:227–240

Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. J Neurosci 22:10914–10923

Robertson EM (2012) New insights in human memory interference and consolidation. Curr Biol 22:R66–R71

Rolls A, Colas D, Adamantidis A, Carter M, Lanre-Amos T, Heller HC, de Lecea L (2011) Optogenetic disruption of sleep continuity impairs memory consolidation. Proc Natl Acad Sci U S A 108:13305–13310

Roman V, Walstra I, Luiten PG, Meerlo P (2005) Too little sleep gradually desensitizes the serotonin 1A receptor system. Sleep 28:1505–1510

Ruskin DN, LaHoste GJ (2009) Reduced-volume cues effectively support fear conditioning despite sleep deprivation. Physiol Behav 96:64–66

Ruskin DN, Liu C, Dunn KE, Bazan NG, LaHoste GJ (2004) Sleep deprivation impairs hippocampus-mediated contextual learning but not amygdala-mediated cued learning in rats. Eur J Neurosci 19:3121–3124

Ruskin DN, Dunn KE, Billiot I, Bazan NG, LaHoste GJ (2006) Eliminating the adrenal stress response does not affect sleep deprivation-induced acquisition deficits in the water maze. Life Sci 78:2833–2838

Sannino S, Russo F, Torromino G, Pendolino V, Calabresi P, De Leonibus E (2012) Role of the dorsal hippocampus in object memory load. Learn Mem 19:211–218

Seibt J, Dumoulin MC, Aton SJ, Coleman T, Watson A, Naidoo N, Frank MG (2012) Protein synthesis during sleep consolidates cortical plasticity in vivo. Curr Biol 22:676–682

Smith C, Rose GM (1996) Evidence for a paradoxical sleep window for place learning in the Morris water maze. Physiol Behav 59:93–97

Sportiche N, Suntsova N, Methippara M, Bashir T, Mitrani B, Szymusiak R, McGinty D (2010) Sustained sleep fragmentation results in delayed changes in hippocampal-dependent cognitive function associated with reduced dentate gyrus neurogenesis. Neuroscience 170:247–258

Sweatt JD (2004) Mitogen-activated protein kinases in synaptic plasticity and memory. Curr Opin Neurobiol 14:311–317

Tiba PA, Oliveira MG, Rossi VC, Tufik S, Suchecki D (2008) Glucocorticoids are not responsible for paradoxical sleep deprivation-induced memory impairments. Sleep 31:505–515

Tobler I, Jaggi K (1987) Sleep and EEG spectra in the Syrian hamster (Mesocricetus auratus) under baseline conditions and following sleep deprivation. J Comp Physiol A Sens Neural Behav Physiol 161:449–459

van der Borght K, Ferrari F, Klauke K, Roman V, Havekes R, Sgoifo A, van der Zee EA, Meerlo P (2006) Hippocampal cell proliferation across the day: increase by running wheel activity, but no effect of sleep and wakefulness. Behav Brain Res 167:36–41

Van Der Werf YD, Altena E, Schoonheim MM, Sanz-Arigita EJ, Vis JC, De Rijke W, Van Someren EJ (2009) Sleep benefits subsequent hippocampal functioning. Nat Neurosci 12:122–123

Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li XY, Descalzi G, Kim SS, Chen T, Shang YZ, Zhuo M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. Nature 461:1122–1125

Vecsey CG, Peixoto L, Choi JH, Wimmer M, Jaganath D, Hernandez PJ, Blackwell J, Meda K, Park AJ, Hannenhalli S, Abel T (2012) Genomic analysis of sleep deprivation reveals translational regulation in the hippocampus. Physiol Genomics 44:981–991

Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11:200–208

Walsh CM, Booth V, Poe GR (2011) Spatial and reversal learning in the Morris water maze are largely resistant to six hours of REM sleep deprivation following training. Learn Mem 18:422–434

Wang GP, Huang LQ, Wu HJ, Zhang L, You ZD, Zhao ZX (2009) Calcineurin contributes to spatial memory impairment induced by rapid eye movement sleep deprivation. Neuroreport 20:1172–1176

Watts A, Gritton HJ, Sweigart J, Poe GR (2012) Antidepressant suppression of non-REM sleep spindles and REM sleep impairs hippocampus-dependent learning while augmenting striatum-dependent learning. J Neurosci 32:13411–13420

Wimmer ME, Rising J, Galante RJ, Wyner A, Pack AI, Abel T (2013) Aging in mice reduces the ability to sustain sleep/wake states. PLoS ONE 8:e81880

Winters BD, Bussey TJ (2005) Transient inactivation of perirhinal cortex disrupts encoding, retrieval, and consolidation of object recognition memory. J Neurosci 25:52–61

Winters BD, Forwood SE, Cowell RA, Saksida LM, Bussey TJ (2004) Double dissociation between the effects of peri-postrhinal cortex and hippocampal lesions on tests of object recognition and spatial memory: heterogeneity of function within the temporal lobe. J Neurosci 24:5901–5908

Yang RH, Hu SJ, Wang Y, Zhang WB, Luo WJ, Chen JY (2008) Paradoxical sleep deprivation impairs spatial learning and affects membrane excitability and mitochondrial protein in the hippocampus. Brain Res 1230:224–232

Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP (2007) A deficit in the ability to form new human memories without sleep. Nat Neurosci 10:385–392

Youngblood BD, Zhou J, Smagin GN, Ryan DH, Harris RB (1997) Sleep deprivation by the "flower pot" technique and spatial reference memory. Physiol Behav 61:249–256

A Bird's Eye View of Sleep-Dependent Memory Consolidation

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Abstract How new experiences are solidified into long-lasting memories is a central question in the study of brain and behavior. One of the most intriguing discoveries in memory research is that brain activity during sleep helps to transform newly learned information and skills into robust memories. Though the first experimental work linking sleep and memory was conducted 90 years ago by Jenkins and Dallenbach, the case for sleep-dependent memory consolidation has only garnered strong support in the last decade. Recent studies in humans provide extensive behavioral, imaging, and polysomnographic data supporting sleep consolidation of a broad range of memory tasks. Likewise, studies in a few animal model systems have elucidated potential mechanisms contributing to sleep consolidation such as neural reactivation and synaptic homeostasis. Here, we present an overview of sleep-dependent memory consolidation, focusing on how investigations of sleep and learning in birds have complemented the progress made in mammalian systems by emphasizing a strong connection between behavior and physiology. We begin by describing the behavioral approach that has been utilized to demonstrate sleep consolidation in humans. We then address neural reactivation in the rodent hippocampal system as a putative mechanism of sleep consolidation. Next, we discuss the role of sleep in the learning and maintenance of song in zebra finches. We note that while both the rodent and zebra finch systems provide evidence for sleep-dependent memory changes in physiology and behavior, neither duplicates the pattern of changes most commonly observed in humans. Finally, we present a recently developed model of sleep consolidation involving auditory classification learning in European starlings, which has the potential to connect

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behavioral evidence of sleep consolidation as developed in humans with underlying neural mechanisms observable in animals.

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Contents

1 A Behavioral Approach to Sleep-Dependent Memory Consolidation

Memory consolidation is a process by which a newly encoded memory is transformed from a labile state to a more stable form. While it has long been established that the transformation from a newly acquired labile memory to a more stable representation takes time, it has become apparent that a period of sleep, rather than time per se, is a critical factor for the consolidation of memories (Walker and Stickgold 2006; Diekelmann and Born 2010; Payne 2011; Rasch and Born 2013). Human studies have employed a standard approach to uncover behavioral evidence of sleep-dependent memory consolidation. Typically, naïve participants receive training and a post-training test on a novel memory task in the morning or evening. The participants then receive a post-retention test 12 h later, after a full-day awake or after an interval that includes a night of sleep, in order to determine whether task performance is better after sleeping retention compared to waking retention. Though comparisons of memory performance across these 12-h retention intervals can begin to indicate a sleep consolidation effect, interpretation of the results is confounded by circadian factors because the training and testing sessions take place at different times of day. Accordingly, performance changes could represent a circadian influence on memory rather than evidence of memory consolidation if the acquisition or performance of a given task naturally varies depending on circadian

time. Consequently, behavioral studies of sleep consolidation often include conditions with morning or evening training sessions followed by a 24-h post-retention test, which eliminates circadian confounds because the training and testing are performed at the same time of day. Therefore, one can behaviorally determine whether sleep is involved in the consolidation of a memory, while ruling out circadian factors by comparing the pattern of performance changes across 12- and 24-h retention intervals. This approach assesses sleep-dependent consolidation in terms of variation in performance across wakefulness and sleep, yet consolidation itself refers to the stability of the memory trace, which may only be indirectly evaluated by task performance.

Investigations of daytime naps additionally provide evidence refuting claims that memory consolidation is merely a time-dependent process that may operate more effectively during sleep due to reduced interference from external sources. Studies have shown that a daytime nap can be as beneficial to memory as a full night of sleep (Mednick et al. 2003; Tucker et al. 2006; Korman et al. 2007; Nishida and Walker 2007). This is a powerful approach because circadian confounds are minimized due to the training and testing taking place at the same time in the nap and no-nap conditions. Moreover, nap studies demonstrate that sleep, rather than time, is the necessary factor because memory benefits can arise over shorter retention periods as long as they include sleep.

Sleep deprivation studies have also helped to refute the time-dependent hypothesis. In these studies, participants are trained on a memory task and deprived of sleep on the first night. Participants then receive a recovery night of sleep on the second night before being retested on the third day. The recovery night of sleep is utilized to mitigate the acute effects of sleep deprivation that necessarily complicate the interpretation of post-deprivation test performance. Studies have found that sleep deprivation after training prevents the expected sleep-dependent performance benefits even after recovery sleep (Stickgold et al. 2000; Fischer et al. 2005; Gais et al. 2006), which challenges the time-dependent hypothesis because memory consolidation should continue throughout sleep deprivation if time, and not sleep, were the critical factor.

Human studies have provided extensive behavioral evidence of sleep consolidation for a multitude of memory tasks using these methodologies. For example, sleep has been shown to benefit associative (Ellenbogen et al. 2006, 2009; Talamini et al. 2008; Rudoy et al. 2009), perceptual (Gais et al. 2000; Fenn et al. 2003, 2013) motor (Walker et al. 2002; Brawn et al. 2010b; Kempler and Richmond 2012), sensorimotor (Robertson et al. 2004; Brawn et al. 2008; Antony et al. 2012), emotional (Hu et al. 2006; Payne et al. 2008), spatial (Ferrara et al. 2008), relational (Ellenbogen et al. 2007), and prospective (Scullin and McDaniel 2010) memory. Furthermore, whereas most studies have entailed the learning of a single novel task, real-world learning often involves the acquisition of a variety of skills or information that may interfere with other learning acquired throughout the day. A number of recent studies have explored the interaction between interference and sleep consolidation (e.g., Walker et al. 2003; Ellenbogen et al. 2006, 2009; Korman et al. 2007; Drosopoulos et al. 2007; Diekelmann et al. 2011; Alger et al. 2012;

Sheth et al. 2012). Remarkably, the memory benefit of sleep is often greater in conditions with interference compared to conditions that only learn a single task. This suggests interference as a useful tool in the design of behavioral experiments of sleep consolidation because interference paradigms could be utilized to magnify sleep effects that may be hidden in simpler experimental tasks. It also provides powerful constraints on neurophysiological models of memory consolidation that could best be explored in animal model systems that exhibit known interference effects.

2 Animal Models of Sleep Consolidation Need Behavior and Brain

Behavioral studies of human memory have provided compelling evidence of sleep-dependent consolidation. The limitations of human research necessitate the development of animal models to uncover the mechanisms underlying sleep consolidation. An attractive animal model would have two principal features: (1) the animal would exhibit performance changes across waking and sleep similar to those observed in humans so that behavioral results in one system would inform experimental design in the other, and (2) experimenters would be able to benefit from technical advantages and physiological analysis of the relevant neural circuits. There are presently several animal models being actively developed in this area, including the extensively studied rodent hippocampal system, and to a lesser degree the development of the mammalian visual system, imprinting in chicks, the learning and maintenance of song vocalizations in zebra finches, and the learning of associative auditory memories in starlings. We assert that none of these models fully meets these criteria, which can be addressed by embracing different research strategies to address deficiencies in each of the systems.

Animal studies have mostly used rats or mice to explore the "standard model" of memory consolidation. This model posits that the hippocampal formation receives input from neocortical regions involved in the encoding of an experience and binds the diverse information into a coherent memory trace. Coordinated reactivations of the newly encoded memory trace are proposed to gradually transfer the memory from a hippocampus-dependent representation to an independent neocortical representation that is integrated with preexisting memories (Frankland and Bontempi 2005; Rattenborg et al. 2011). The process of memory transfer via memory reactivation is believed to depend on sleep. In support of this model, numerous studies have reported that the firing patterns expressed in hippocampal place cells of rats trained to move through spatial environments (e.g., linear tracks or open fields) are reactivated during subsequent sleep (e.g., Wilson and McNaughton 1994; Kudrimoti et al. 1999; Lee and Wilson 2002). Moreover, hippocampal reactivations have been found to coincide with reactivations in the visual cortex (Ji and Wilson 2007) and medial prefrontal cortex (Peyrache et al. 2009). These coordinated sleep reactivations have been interpreted as evidence of a memory transfer from the

hippocampus to cortical areas involved in the initial encoding of the experience (Marshall and Born 2007; Rasch and Born 2007; O'Neill et al. 2010).

Sleep reactivations, however, could be recruited by a variety of mechanisms that invoke correlated network activity or could be incidental to those mechanisms, and by themselves are not conclusive evidence of memory consolidation. Though it is well established that waking experiences can alter brain activity during subsequent sleep, the relationship between sleep reactivations and memory consolidation is tenuous without behavioral evidence demonstrating that sleep reactivations produce some memory benefit for the animal. Yet, many studies of sleep reactivations have not included behavioral measures of memory to compare pre- and post-sleep performance levels. For example, evidence of sleep reactivation has typically been found after rats have been over-trained on spatial tasks such as moving along a linear track (e.g., Lee and Wilson 2002) or running to a sequence of locations (Euston et al. 2007). Consequently, it is difficult to relate the sleep reactivations to memory consolidation because the spatial memory in these cases had presumably been consolidated during the days or weeks of prior training.

Studies that have involved learning on a new task as opposed to performing an over-trained task have also failed to connect changes in neural activity to behavioral measures of sleep consolidation. For instance, learning odor–reward associations was found to increase sleep spindle density (Eschenko et al. 2006) and hippocampal sharp-wave ripple activity (Eschenko et al. 2008) during post-training sleep, both of which are associated with hippocampal reactivations. In another study, learning a new rule about reward location resulted in sleep reactivations in the medial prefrontal cortex after the rule had been learned (Peyrache et al. 2009). Finally, playback during sleep of sounds associated with reward location biased hippocampal reactivations such that playback produced reactivations indicative of movement toward the reward location (Bendor and Wilson 2012). Despite these intriguing findings, task performance in each case was not tested after sleep to show that the sleep reactivations improved or stabilized the recently acquired memories.

A few studies have incorporated pre- and post-sleep behavioral measures of spatial tasks into investigations of sleep reactivations. In one case, an increase in hippocampal sharp-wave ripples was correlated with performance on a place–-reward association task (Ramadan et al. 2009). In two other studies, sharp-wave ripples (and the associated hippocampal reactivations) were disrupted via electrical stimulation, which produced performance decrements compared to control conditions on a place–reward association task (Girardeau et al. 2009) and a spatial navigation task (Ego-Stengel and Wilson 2010). In each case, however, the performance benefits of allowing undisturbed sleep reactivations only materialized after several days of training and testing, which make it difficult to determine the respective influence of sleep, wakefulness, and repeated experience with the task. Collectively, these studies have strengthened the connection between sleep reactivations and memory consolidation, yet the behavioral effects of sleep on spatial memory in rodent models of neural reactivation are rather weak compared to the broad range of human studies demonstrating clear memory benefits after a single bout of sleep.

Behavioral evidence in other hippocampal-based memory tasks has additionally supported a role for sleep in rodent memory using sleep deprivation protocols. For example, fear-conditioned mice expressed a contextual fear memory 24 h later if they were allowed undisturbed sleep after training but not if they were sleep-deprived for 5 h immediately after training (Graves et al. 2003). Likewise, 6 h of sleep deprivation during the rest period or 12 h (but not 6 h) of sleep deprivation during the active period prevented contextual fear memory in rats when tested 24 h later, suggesting that the memory disruption depended on the total amount of sleep that was lost (Hagewoud et al. 2010). In the object–place recognition task, rats that were trained at the beginning of their rest (morning) or active (evening) period and retested after a 2-h retention interval (with or without sleep deprivation) only retained the object–place memory if they were allowed undisturbed sleep in the morning (Binder et al. 2012). Likewise, rats retained an object–place memory after 80 min of sleep but not after 80 min of sleep deprivation during the rest period or 80 min of wakefulness during the active period (Inostroza et al. 2013).

Though these studies support a role for sleep in the consolidation of rodent memory, there are some limitations when compared to the more rigorous behavioral methods employed in human studies of sleep consolidation. Importantly, these studies are based on sleep deprivation protocols. Evidence of impaired memory after sleep deprivation is not the same as demonstrating that sleep consolidates memory because the stress and other non-specific effects attendant to sleep deprivation cannot be ruled out as contributing factors to the memory loss. While the failure to consolidate a memory after sleep deprivation might indicate that the memory failed to consolidate because the mechanisms of consolidation could not be completed without sleep, it is also possible that: (1) the memory did consolidate, but the ability to express the memory was impaired due to the animal behaving in a sleep-deprived or sleep-restricted state, or (2) the memory failed to consolidate because the deleterious effects of the sleep deprivation itself altered the natural process of consolidation.

Sleep deprivation paradigms are practical for rodent studies because rodents frequently sleep during both their rest and active periods. Consequently, it is difficult to instantiate a wake-retention period that does not also include sleep. For example, a contextual fear-conditioning study that was modeled after the standard design of human sleep consolidation studies trained mice in the morning or evening and tested after 12 or 24 h (Cai et al. 2009). Only mice in the 12-h "wake" condition failed to consolidate the contextual fear memory. While this pattern of results suggests a role for sleep in the consolidation of contextual fear conditioning, mice in the "wake" condition slept for ~3–4 h during the retention interval. This lack of sleep-dependent memory benefit across an interval with multiple hours of sleep is in stark contrast to human behavioral studies showing that even naps can be as beneficial as a full night of sleep (e.g., Mednick et al. 2003).

Finally, the type of learning examined in most rodent studies is, appropriately for hippocampal research, related to declarative memories, but many human behavioral studies of sleep-dependent memory consolidation are of non-declarative memories such as various forms of skill learning. It remains an open question whether the

patterns of changes observed in humans learning skills can be assumed to obtain in the rodent hippocampal models. These limitations could be addressed by more vigorous studies to directly connect the behavioral observations in rodents with those of humans, which would allow examination of the extraordinarily rich rodent physiological data in a better-defined context. We predict that achieving such results would have a saltatory effect on the field.

3 A Comparative Approach to Memory Consolidation: Bird Brains and Bird Sleep

We now turn to the study of sleep and memory in birds, embracing the comparative approach. As with all "non-traditional" model systems, this engenders knowledge of specialized techniques and a distinct literature. Here, we begin with a description of avian brain organization and avian sleep.

A long-standing misconception concerning the organization of the avian brain has recently been revised to better reflect the relationship between avian and mammalian brains (Reiner et al. 2004a, b, 2005; Jarvis et al. 2005). The avian cortex is organized into distinct nuclei as opposed to the layered organization of mammalian neocortex. Though early work erroneously proposed that the entire avian pallium was a hypertrophied striatum, a reevaluation of avian neuroanatomy using molecular, physiological, and anatomical methods has identified homologies between avian cortex and mammalian neocortex, placing avian studies into a more meaningful mammalian context. Whereas hodological and histological markers have identified a circumscribed region of the pallium as the avian striatum, other regions of the avian cortex contain a series of sensory and motor pathways comparable to the canonical neocortical circuit in mammals. These pathways include granule cell layers that receive ascending input from different dorsal thalamic nuclei. Projections from the granule cell layers lead to secondary neurons (similar to neocortical layer 2/3 neurons), which lead to neurons projecting out of the cortex (similar to neocortical layer 5 neurons). Even patterns of radial, columnar-like connectivity have recently been found to span the avian auditory cortex (Wang et al. 2010). Moreover, layer-specific molecular markers of the mammalian neocortex are selectively expressed in the corresponding structures of the avian cortex (Dugas-Ford et al. 2012), and the avian forebrain, like the mammalian cortex, receives ascending modulatory input from the brainstem, midbrain, and basal forebrain (Ball and Balthazart 2010). Nonetheless, determining the precise relationship between avian and mammalian brains is an ongoing project, and different interpretations have been proposed within this modern framework (e.g., Belgard et al. 2013; Belgard and Montiel 2013; Finger et al. 2013; Montiel and Molnar 2013).

The homology between avian and mammalian cortical structures highlights the value of comparative studies of avian sleep. Sleep is a complex state that is defined in terms of behavioral, physiological, electrophysiological, and homeostatic characteristics. Though a sleep-like state has been observed in most, if not all, animals

studied (Cirelli and Tononi 2008; but see Siegel 2008), the attribution of sleep in reptiles, amphibians, fish, and invertebrates is largely based on behavioral criteria such as periods of behavioral quiescence, increased arousal thresholds, and species-specific sleep postures or sleep sites. Birds and mammals are the only taxonomic groups that additionally express the electrophysiological features of slow-wave sleep (SWS) and rapid-eye movement sleep (REM). Birds and mammals are also the two taxonomic groups of animals with the largest and most complex forebrains (Rattenborg et al. 2009).

The structure of sleep in many avian species has been examined with EEG recordings (reviewed in Campbell and Tobler 1984; Amlaner and Ball 1994; Rattenborg and Amlaner 2010). Avian sleep generally consists of non-REM (NREM) sleep interspersed with brief periods of REM activity (Fig. 1). NREM sleep includes SWS, which is characterized by large amplitude activity in the delta (1–4 Hz) frequency range. Although many studies categorize sleep in animals as a dichotomy between REM and SWS (i.e., SWS and NREM are used interchangeably), birds can also exhibit a transition state that contains electrophysiological features that are intermediate between SWS and REM (Low et al. 2008). The

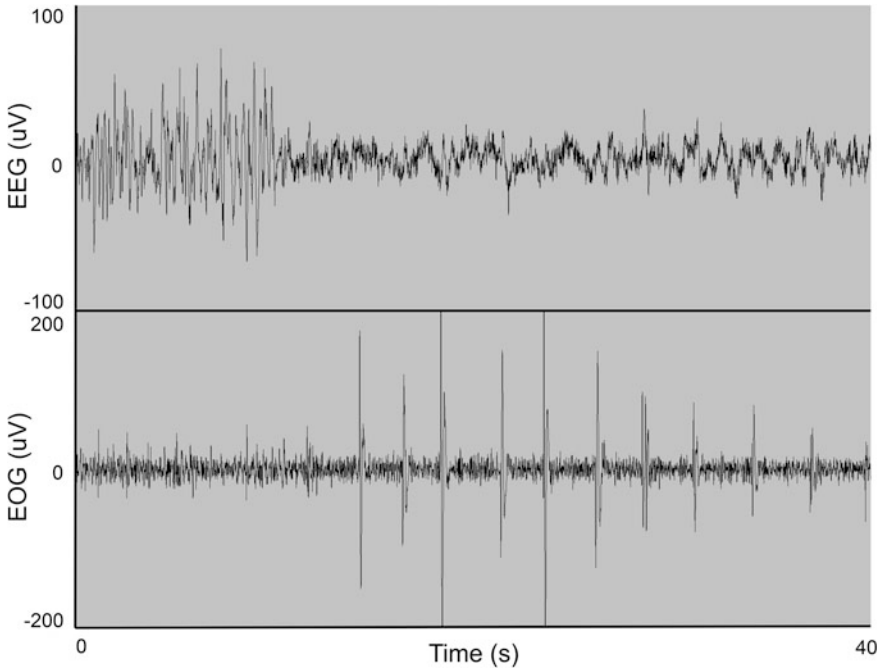

Fig. 1 Starling sleep. A 40-s trace of EEG and EOG recordings from a sleeping starling is shown. The first ~10 s of the EEG signal shows low-frequency, high-amplitude waves characteristic of slow-wave sleep with minimal eye movement in the EOG signal. The EEG signal then rapidly transitions to high-frequency, low-amplitude waves characteristic of REM sleep with associated rapid-eye movements appearing in the EOG signal seconds later (T. Brawn, unpublished data)

amount of SWS in birds, as in mammals, is relatively high early in the night and decreases across sleep (Low et al. 2008; Martinez-Gonzalez et al. 2008). Birds, like marine mammals, are capable of unihemispheric SWS, during which one hemisphere displays a wake-like EEG pattern and the other hemisphere displays electrophysiological signs of SWS (reviewed in Rattenborg et al. 2000). Early reports did not find evidence for SWS homeostasis in birds; however, more recent studies have compellingly demonstrated a homeostatic response to sleep deprivation (Jones et al. 2008; Martinez-Gonzalez et al. 2008), which warrants additional study of other avian species. Despite similarities between avian and mammalian NREM sleep, thalamocortical sleep spindles and hippocampal sharp-wave ripples, both prominent electrophysiological markers of mammalian NREM sleep that are thought to be important for sleep-dependent memory consolidation, have yet to be discovered in birds (reviewed in Rattenborg et al. 2011). Nevertheless, birds clearly exhibit sleep-dependent memory consolidation.

REM sleep in birds is characterized by a desynchronized low-amplitude, high-frequency EEG pattern similar to the waking state. While rapid-eye movements during REM sleep are common, the muscle atonia that is a defining feature of REM sleep in most mammals is less consistent in birds. Additionally, the duration of REM sleep episodes is shorter in birds than in mammals, lasting from a few to tens of seconds. The brief duration of REM sleep episodes has likely led to an under-reporting of REM sleep in earlier investigations of avian sleep (see Lesku et al. 2009 for a discussion of scoring sleep states in birds). For instance, REM sleep in the zebra finch was originally reported as averaging 0.2 h per 24-h period (Schmidt et al. 1990). In contrast, a more recent study that included sophisticated automated techniques confirmed by extensive manual scoring reported that zebra finches spent 23 % of an 8-hour dark period in REM sleep (Low et al. 2008). Like mammals, the amount of REM sleep is relatively low early in the night and increases as sleep continues (Low et al. 2008; Martinez-Gonzalez et al. 2008).

The few recent studies of avian sleep have shown a systematic variation of SWS and REM sleep across the night. Indeed, a study of sleep in adult male zebra finches found an ultradian pattern characterized by a decrease in SWS (from 50 to 25 %) across the night in conjunction with an increase in the percentage of REM sleep (from 8 to 30 %) as well as an increase in the average duration of REM sleep bouts (from 7 to 15 s) (Low et al. 2008). Preliminary results (T. Brawn, unpublished) indicate similar dynamics including a high density of REM sleep in another passerine species, the European starling, which contrasts with earlier studies of starling sleep (Szymcazk 1985, 1986). Whether there is a difference between songbirds and non-passerine species remains unresolved. A recent molecular phylogeny places psittaciformes (parrots) as the sister group to passerines (Hackett et al. 2008). Though the only studies of parakeet sleep reported very low levels of REM (Ayala-Guerrero et al. 1988; Ayala-Guerrero 1989), the recordings were made under conditions of constant (24 h) light, which may not be representative of sleep in birds experiencing a natural light/dark cycle.

The patterns of avian sleep in recent studies are largely consistent with how sleep is described in mammals. However, it is necessary to recall that there is no single pattern of sleep for mammals; rather there are vast differences in the duration and structure of sleep across the range of mammalian species. This is obvious even when only considering the most common subjects of mammalian sleep studies: rats, cats, and humans. Such considerations indicate a compelling need for additional comparative work in birds, especially when considering that many studies of avian sleep were conducted decades ago and will likely need to be revised to reflect advances in recording technologies, computational methods for sleep-stage analysis, and a greater understanding of the structure of sleep in birds.

4 An Introduction to the Birdsong System

There are ~10,000 species of birds. Whereas all birds can produce innate calls, only songbirds (~4,000 species), parrots (~350 species), and hummingbirds (~350 species) can learn to produce vocalizations. Studies in the songbird species zebra finch (*Taeniopygia guttata*) have provided the most extensive evidence in birds linking sleep to learning and memory consolidation. All true songbirds (i.e., oscine passerines) express specialized forebrain nuclei necessary for song learning and production. The "motor" pathway, which is required for singing, consists of direct projections from the sensorimotor cortical nucleus HVC to the motor output nucleus RA. The "anterior forebrain pathway" (AFP), which is required for song learning, also begins in HVC and ends with projections to RA. This pathway, however, additionally includes the basal ganglia components of the song system in Area X (Farries and Perkel 2002; Carrillo and Doupe 2004; Farries et al. 2005) and represents a cortico-basal ganglia-thalamocortical pathway. The AFP, which gives rise to variability in vocalizations (Sohrabji et al. 1990; Scharff and Nottebohm 1991; Kao et al. 2005; Ölveczky et al. 2005), is the primary source of RA excitation during early development. This likely explains the highly variable vocalizations that are produced in young juveniles (Aronov et al. 2008). The influence of the AFP on song production, however, changes during development, with the AFP having a minimal direct influence on adult singing. The AFP, nonetheless, is involved in regulating auditory feedback (Brainard and Doupe 2000) and may contribute to the sleep-related regulation of singing (Andalman and Fee 2009). After receiving input from the motor and AFP pathways, RA projects to brainstem structures involved in syringeal and respiratory control. These brainstem structures, along with higher-order auditory structures, feedback onto HVC. Neurons in RA have been the focus of several studies relating song system physiology with singing behavior and are known to express sleep-dependent features, as described below.

5 Sleep and Developmental Song Learning in Zebra Finches

The song learning process in zebra finches begins during the altricial phase of development. During this phase of song learning, a juvenile zebra finch forms a sensory memory of the "tutor" song produced by its father or a different adult male conspecific. This sensory memory has traditionally been viewed as a "template" or comparator that guides vocal learning (Adret 2004). In spite of extensive research effort, unambiguous identification of this comparator remains unresolved. Physiological processes related to the template include immediate early gene (IEG) expression and related signaling pathways in the auditory system early in development (Terpstra et al. 2005; London and Clayton 2008), single neuron selectivity for tutor song in HVC early in development (Adret et al. 2012), single neuron selectivity for tutor song in the AFP at intermediate stages of development (Solis and Doupe 1999), reversible lesion studies of the AFP (Aamodt et al. 1996), and others. Gobes et al. (2010) demonstrated IEG expression related to tutor song acquisition but only in higher-order auditory areas. No expression was detected in song system nuclei. When single neuron recordings were made in the HVC of presinging birds, however, a small population of neurons was detected that was selective to the tutor song (Adret et al. 2012). The selectivity of those neurons for song was highly significant compared to other adult conspecific songs including the familiar songs of birds from neighboring cages. Such a small population would be difficult to detect in bulk IEG expression studies.

Collectively, these results indicate a broad distribution of structures expressing effects of tutor song exposure. This argues that even if there is a single structure that acts as the primary site of the template, this memory is rapidly distributed throughout the song system. Such memory transference is a hallmark of sleep-dependent memory consolidation, and it is a viable conjecture that memorization of the tutor song is a sleep-dependent phenomenon. Whereas a role for sleep in the sensory memory formation of the tutor song has not been directly tested, nonetheless, isolated juveniles have been observed to rapidly fall asleep upon their first exposure to a singing adult (T. Lints, unpublished data from the Tchernichovski lab; P. Adret, unpublished data). Though speculative, this supports the suggestion that sleep could be important to this process and would be consistent with sleep consolidation studies of sensory memory in humans.

The first song-related vocalizations begin during the sensorimotor phase of song learning. Initially, juvenile birds produce subsong, which consists of relatively long and variable sequences of unstructured sounds, a process similar to babbling in human infants. Despite the relative lack of structure in subsong, these vocalizations have greater spectrotemporal complexity and variability than innate calls, which are distinct from song. Subsong transitions into plastic song, in which vocalizations become more structured such that sequences of individual syllables become recognizable but lack the stereotypy of adult song. The plastic song continues to be modified as it approaches an increasingly accurate imitation of the tutor song. The

bird finally produces a crystallized song, which is characterized by temporal and spectral stereotypy, at the time of sexual maturity. The process of developmental song learning has been extensively studied, and numerous detailed reviews are available (e.g., Marler 1997; Margoliash 2002; Lipkind and Tchernichovski 2011).

Although song learning has long been studied, compelling evidence that sleep plays a critical role in the sensorimotor phase of song learning has only recently been described, and to date, this has only been established in zebra finches. To bring the process of developmental song learning under experimental control, a juvenile bird is raised by its non-singing mother in a sound isolation chamber to enable high-quality vocal recordings. When the juvenile becomes independent, it is given access to a tutor song by pecking a key or pulling a string (Tchernichovski et al. 2001, 2004). Though this differs from the natural developmental process in which zebra finches live in groups and learn from adult male tutors, this paradigm controls for the variation in singing behavior by the tutor and the social interactions between the juvenile and tutor that would otherwise occur. A juvenile bird in this paradigm is first exposed to a tutor song at ~40 days post-hatch.

A circadian variation in singing rapidly emerges such that vocalizations early in the day have less structure than vocalizations later in the day, a pattern that continues but attenuates throughout the song learning process. Accordingly, songs that are produced in the afternoon have more spectrotemporal complexity and are more accurate copies of the tutor song than vocalizations from the previous or subsequent mornings. Moreover, preventing juveniles from singing in the morning results in songs with less structure when they are allowed to sing in the afternoon. Conversely, a bout of sleep during the day leads to a second round of lower structure songs. Thus, sleep is affecting behavior in a seemingly inverse fashion, whereby the songs sung early in the day are less complex than songs produced later in the day. This circadian pattern is directly related to sleep and is instrumental in the song learning process. Critically, juveniles that ultimately produce the most accurate copies of the tutor song are those that had that greatest magnitude of circadian variation during the sensorimotor phase of song learning (Derégnaucourt et al. 2005). This result seems counter-intuitive to the typical effects of sleep on learning and memory. However, juvenile vocalizations are highly variable, especially early in development. Because the song learning process involves extensive daily practice over ~60 days, the reduction in song complexity across sleep may be a mechanism to prevent juvenile birds from prematurely crystalizing song features that do not accurately represent the tutor song. The pattern itself may arise as an interaction between sensory memories and motor memories, both of which may be changing as birds learn to sing (see below). This emphasizes the sensorimotor nature of birdsong learning, which is distinct from the perceptual, procedural, or episodic memories more commonly studied in humans.

Examining the firing properties of RA (primary motor cortex analog) during sleep has further confirmed a role for sleep in song learning. Prior to tutor song exposure, neurons in RA expressed low spontaneous rates with little bursting, which could be represented by a unimodal interspike interval (ISI) histogram. However, the ongoing discharge profile of RA was significantly altered on the first

night of sleep after tutor song exposure. There was an increase in short-interval ISIs, many of which were organized into protobursts, and the ISI histogram became bimodal. It seems plausible that the sleep bursting in RA is part of the causal mechanism driving the circadian variation in singing because the circadian singing pattern only materialized on the morning after the sleep bursting emerged. The birds in these experiments were exposed to one of three different tutor songs, and the average ISI histogram for each bird was similar for birds trained on the same tutor song and different from birds trained on the other tutor songs. The shape of the ISI histogram, however, was dynamic such that the firing properties of RA during sleep exhibited corresponding changes in the ISI histograms when birds were switched from one tutor song to another. The dynamic nature of the ISI distributions that characterize the different tutor songs suggests that the information represented in the sleep bursting was directly related to the tutor song rather than to the subsong vocalizations of the juvenile birds (Shank and Margoliash 2009). RA neurons begin to express auditory responses during sleep only once a juvenile bird transitions from subsong to plastic song (M. Lusignan, unpublished data), which also coincides with HVC taking over from the AFP as the predominant driver of RA activity. At this point in development, RA responds selectively to the playback of the bird's own song during sleep.

The effect of sleep (as assessed by depth of circadian variation) is strongest when RA is driven by the AFP and when singing is most variable. The nighttime activity of the RA motor neurons at this early time in development expresses the sensory memory. A theory that consolidates all these observations is not yet within reach. But we note that in contrast to other systems, this one expresses the interactions of sensory and motor memories, both changing over the time course of development. We speculate that these two memories both induce changes in singing behavior but at different phases (sleep and singing), and the interaction between the two processes is less coordinated early in development. We further speculate that the sensorimotor mappings of HVC-RA pass a critical threshold that enables populations of HVC-RA neurons to provide structured input into RA during sleep, which transmits auditory information from HVC to RA and drives sleep bursting starting at the onset of plastic singing.

Finally, song learning in zebra finches is not the only learning phenomenon in juvenile birds for which sleep is essential. The consolidation of visual imprinting in the (non-songbird) domestic chick (*Gallus gallus domesticus*) also relies on sleep. Young visually naïve chicks can learn the visual characteristics of a conspicuous object (i.e., the imprinting stimulus, or IS) upon exposure. Once imprinted, chicks will approach and direct social behaviors toward the imprinted object but not toward novel objects. After exposure, IS-selective neurons begin to emerge in the intermediate and medial mesopallium. In one study, the maximal proportion of IS-selective neurons was observed at 25 h after IS exposure. The largest increase in IS-selective neurons occurred between 8 and 25 h after exposure, which indicated a possible role of sleep in the consolidation of the IS memory (Horn et al. 2001). Later work confirmed the necessity of sleep. Indeed, chicks that were allowed undisturbed sleep after exposure had significantly more IS-selective neurons at

19.5 h post-exposure than chicks whose undisturbed sleep was delayed by 7.5 h. Though sleep states were not scored, an increase in EEG power in low frequencies (0–6 Hz) was observed during the sleep period. Furthermore, only chicks that were allowed undisturbed sleep immediately after the IS exposure expressed a behavioral preference for the IS when tested 20 h later (Jackson et al. 2008). Overall, studies of juvenile zebra finches and domestic chicks have demonstrated an essential role of sleep in the consolidation of two distinct critical-period learning phenomena, which shares similarities with the effects of sleep on language-learning tasks in human infants (Gomez et al. 2006; Hupbach et al. 2009).

6 Sleep and Adult Song Maintenance in Zebra Finches

Skilled behaviors require continued practice to be maintained at a high level of performance, a process that perhaps involves sleep. Zebra finches produce remarkably stereotyped songs throughout their adult lives. One explanation for this consistency is that zebra finches perform their song extensively each day. Another contributing factor may be subtle modifications to the firing properties of RA neurons during sleep that affect daytime singing behavior.

One proximate mechanism for regulating daytime behavior by nighttime processes is modification of neuronal replay. Neuronal replay refers to offline activity of single neurons or neural populations that produce approximate copies of the patterns of neuronal activity observed during waking behavior. Though replay can occur during wakefulness, it has most commonly been detected during sleep. To demonstrate sleep replay, it is necessary to compare neural activity during a specific behavior with the neural activity of the same neuron or population during sleep. Perhaps the most compelling example of veridical sleep replay at a single neuron level is that of RA neurons in adult zebra finches (Dave and Margoliash 2000) (Fig. 2). These neurons, which emit precisely timed bursts every time a motif is sung, occasionally burst while zebra finches sleep. Bursts occurring at different parts of the song have differences in the number or timing of spikes within the bursts. Because the variation of spikes within a burst associated with one part of the song is much lower than the differences in bursts related to other parts of the song, RA neurons have unique bursts, which has facilitated the detection and analysis of neural replay during sleep. In a study of sleep replay, a burst was defined as a sequence of interspike intervals that fell outside the non-bursting distribution. Approximately 7 % of RA spikes during sleep were part of a burst, and 15 % of sleep bursts matched a burst that the neuron emitted while the bird was singing (Dave and Margoliash 2000). These estimates, however, represent a lower bound on sleep bursting because for statistical reasons only long bursts (8 or more spikes) were analyzed. Moreover, a sleep burst was only considered to match a singing burst if the precise timing of individual spikes within the bursts matched, yet the relation between singing and sleeping bursts was often compelling even if a subset of spikes within a burst differed. Furthermore, bursting tends to synchronously

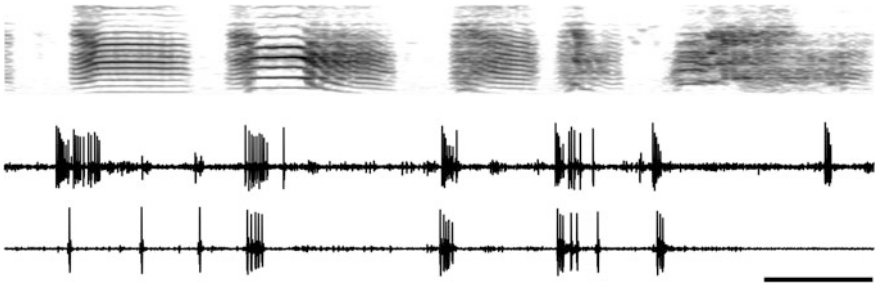

Fig. 2 Neuronal replay in the zebra finch song system. A spectrogram (frequency vs. time) of zebra finch song is shown in the top panel, with two 900-ms raw traces of activity of a single RA neuron below. The top trace of neuronal activity was recorded at the same time the bird sang the motif displayed above it. Note the bursting activity, which is characteristic of RA activity during singing. The bottom neuronal trace is of spontaneous discharge activity recorded while the bird slept at night. Note that after three single spikes (typical of background or resting activity during sleep), the neuron began to burst, with the timing and structure of the bursts closely approximating the activity of the neuron during singing. A statistical analysis of individual spike bursts (not considering trains of spike bursts such as are displayed in the figure) demonstrated that such matches occurred at a statistically significant level in 13/14 neurons tested (Dave and Margoliash 2000). Scale bar, 100 ms

recruit many neurons within the song system, which suggests that the amount of RA sleep bursting that represents replay would be higher with simultaneous single-cell recordings of a population of RA neurons.

The replay of a specific waking behavior indicates that precise information is represented in neural activity during sleep. If sleep replay is a mechanism of memory consolidation, then patterns of neural activity should change across sleep in a manner that is adaptive to learning and memory. Taking advantage of the reliability of RA activity during singing, a recent study reported systematic changes in the bursting properties of individual neurons that were recorded during singing and that were maintained across periods of sleep (Rauske et al. 2010). The structure of 33 of 115 bursts (28.7 %) changed across sleep. By comparison, only 18 of 551 bursts (3.3 %) exhibited similar changes across daytime singing. The primary change was a loss in the number of spikes per burst after sleep (Fig. 3), yet the interspike intervals for the altered bursts increased such that the overall burst duration remained approximately constant. Half of the recorded neurons expressed at least one burst change when comparing pre- and post-sleep singing.

Though the changes to burst structure may be subtle, the accumulated changes over one night, let alone over the lifespan of the bird, would drastically impair a zebra finch's song if there were not a compensatory response to add spikes back into the population. Given the stability of adult zebra finch songs, how do spikes get back into the system? This is the subject of speculation because to date spike gain has yet to be experimentally observed. On the one hand, zebra finches sing their unique motifs (relatively fixed sequences of syllables) upward of 1,000 times per day. This intensive practice likely potentiates the synapses in RA, which could lead

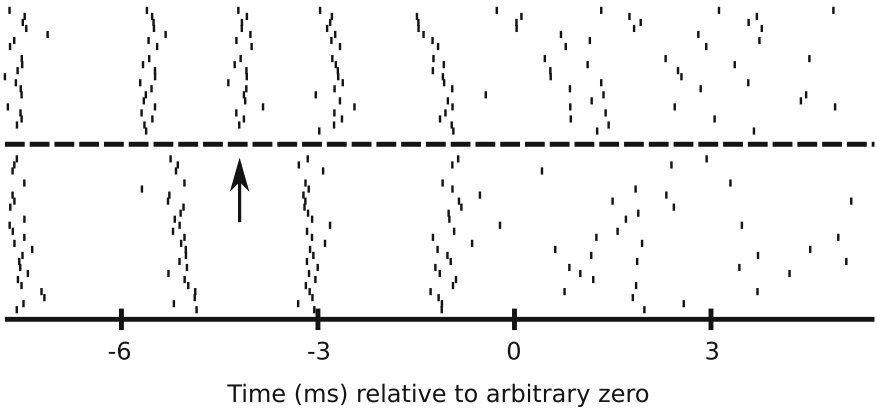

Fig. 3 RA neurons lose spikes across sleep. An example of changes across sleep in the pattern of activity of one burst from an RA neuron is shown. Each tick mark represents the timing of one spike, relative to a zero time established to align the data across multiple renditions of the motif that the bird sang. The burst comprises multiple spikes emitted over a period of approximately 15 ms. The neuron was recorded for 20 renditions of the motif prior to when the bird slept for approximately 140 min (*dashed line*). The neuron was then recorded for an additional 25 motifs after the bird awoke and began to sing again. Note that the third spike (at the *arrow*) in the pre-sleep structure of the burst is missing in the post-sleep structure of the burst, representing a change in burst structure and a loss in spikes following sleep

to an increase in the number of spikes emitted. On the other hand, neurogenesis is known to take place within the song system, specifically involving neurons projecting form HVC to RA (Goldman and Nottebohm 1983). New neurons, which are initially incorporated into local HVC circuits (Paton and Nottebohm 1984), project to and synapse in RA in 1–2 weeks (Alvarez-Buylla et al. 1988). A steady addition of synapses from HVC could also counteract the nightly loss of spikes in RA neurons. This phenomenon of losing spikes across sleep and gaining spikes across wakefulness may represent an instantiation at the single neuron level of the synaptic homeostasis hypothesis (Tononi and Cirelli 2003, 2006). Alternatively, each night many neurons in RA may lose spikes (loss of drive from HVC), but only some would be driven below a threshold where they can accept new inputs from HVC (perhaps arising from afferents of recently born HVC neurons recently arrived in RA). Under this hypothesis, if the number of neurons losing spikes at night were much greater than the number gaining spikes at night, the latter would be difficult to detect in challenging physiological recordings.

The loss of spikes within RA bursts was first observed during sleep rather than when the bird began singing in the morning. The structure of the modified sleep bursts was more similar to the bursts that would occur during singing on the following day compared to the bursts that occurred during singing on the previous day (Z. Chi, unpublished results). Accordingly, the activity of RA during sleep includes a “preplay” component that is predictive of future neural activity rather than a recapitulation of past activity. This finding of preplay coincides with recent

work in the rodent hippocampal system that has also uncovered instances of sleep preplay (Dragoi and Tonegawa 2011, 2013). This suggests the need for a reevaluation of the literature on offline reactivations to determine whether replay and preplay are distinct phenomena or whether the many reports of reactivation of previous waking behavior would be more accurately described as preplay of future waking activity.

The study of RA activity during sleep offers a significant opportunity that is largely untapped to explore the development and function of sleep replay in relation to a known and stable behavior (i.e., the bird's stereotyped song). The presence of sleep replay (or preplay) in RA also indicates that the reactivation of waking neural activity during sleep extends beyond the hippocampal memory system and therefore may be a mechanism of memory consolidation that generalizes to other memory systems. Nonetheless, the studies of sleep replay in zebra finches share an important weakness with the studies of rodent sleep reactivation. Namely, the replay phenomenon in RA is not directly connected to behavioral evidence of learning and memory. In juveniles, the sleep bursting activity in RA is not necessarily a replay of waking activity. Indeed, the lack of song stereotypy and precise RA activity make detecting replay at this stage of development difficult, but it also offers an opportunity to track the emergence of replay phenomena in a developing system. Likewise, there is not a direct connection between sleep replay and song maintenance in adults. From the neural perspective, the replay of singing neural activity occurs during sleep, and the bursting properties of individual neurons change across sleep. From the behavioral perspective, adult zebra finch song remains remarkably stable from day to day. Nonetheless, a causal relationship between replay (or preplay) and the maintenance of adult song has yet to be fully established.

7 A New Animal Model of Sleep Consolidation: Auditory Classification Learning in European Starlings

A dichotomy between human and animal research of sleep consolidation has persisted. Human studies have provided convincing behavioral evidence that retention intervals with sleep benefit memory compared to similar periods of wakefulness. In conjunction with imaging and polysomnography, human studies have additionally been able to localize memory representations to specific brain regions, identify how those memories are reorganized across brain regions after sleep, and relate performance changes to specific electrophysiological features of sleep. Nonetheless, human studies are limited at determining the underlying neuronal, molecular, and genetic mechanisms that are responsible for sleep-dependent memory benefits. Animal studies, on the other hand, have provided data that could be the underlying basis of sleep consolidation. While sleep deprivation has been shown to impair memory consolidation in animals, there is still limited behavioral evidence showing that sleep, compared to natural wakefulness, benefits recently acquired memories in

adult animals as is commonly observed in humans. To address this, we developed an auditory classification learning paradigm in European starlings (*Sturnus vulgaris*) that was modeled after the standard behavioral approach of human studies of sleep consolidation.

Starlings are a songbird species with complex vocalizations consisting of long sequences of temporally discrete motifs, with each motif lasting ~1 s and being composed of a sequence of shorter syllables (Adret-Hausberger and Jenkins 1988; Eens 1997). Whereas zebra finches only learn a single motif that becomes crystallized around 90 days post-hatch, starlings are open-ended learners that continue to add new motifs to their repertoire throughout their lives, including the incorporation of sounds produced by different species of songbirds, other animals, and environmental noises. A bout of starling song can be wondrously complex, but tends to follow an overall structure. Starlings begin with introductory notes followed by a sequence of some of the motifs within a starling's repertoire, with each motif being produced one or more times. "Warbles" (a category of motifs) tend to appear earlier in a song bout, followed by a transition to the "rattle" category of motifs, and singing often terminates with loud high-frequency whistles. A single song bout may last between 30 and 120 s, and no two song bouts are likely to be the same.

Wild starlings maintain large repertoires of unique motifs, and starlings can learn to identify individuals by associating the production of certain motifs with specific individuals (Gentner and Hulse 2000; Gentner et al. 2000). Starlings are also very adaptable to laboratory caging and can be trained with operant techniques to classify auditory stimuli through differential reinforcement of responses to different stimuli. In the Go/No-Go paradigm, starlings are rewarded with food when they respond to the "Go" stimulus, whereas the cage lights are turned off when they respond to the "No-Go" stimulus. Over the course of training, starlings learn to respond to the Go stimulus and withhold response from the No-Go stimulus, demonstrating the ability to learn and maintain auditory classifications. The behavioral importance of song recognition for starlings along with the ease in which they can perform operant learning tasks in the laboratory makes starlings an attractive model system for studying auditory perceptual learning and associative memory.

In an early experiment, we investigated whether adult starlings express behavioral evidence of sleep consolidation in a manner similar to what has been observed in humans. The starlings first completed 4 conditions in which they learned to classify pairs of 5-s segments of novel starling song. The starlings were then tested immediately after the training session and again after a retention period that consisted of wakefulness or that included sleep. Classification performance in the "wake" condition, wherein starlings were trained in the morning and retested in the evening, decreased non-significantly from the post-training test to the post-retention test (Fig. 4a). In contrast, starlings in the "sleep" condition, which were trained in the evening and retested the next morning, exhibited a significant performance improvement across the night of sleep. Classification performance also improved significantly across 24-h retention intervals regardless of whether starlings were

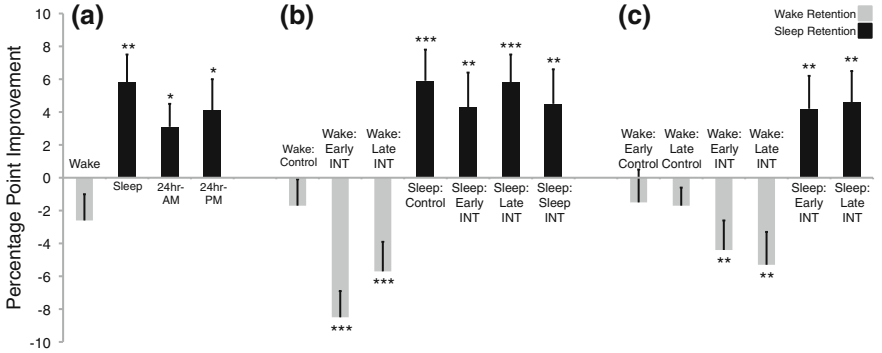

Fig. 4 Auditory classification performance improvement in starlings. Starlings were trained to classify two 5-s segments of novel starling song and retested after retention period that consisted of wakefulness (*gray bars*) or that included a night of sleep (*black bars*). Performance improvements scores were calculated as the difference between the post-retention and post-training test scores. Data are means ±SEM (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). Data in part **a** are from Brawn et al. (2010a). Data in parts **b** and **c** are from Brawn et al. (2013)

trained in the morning or evening. This pattern of results was then replicated in two conditions that entailed post-tests after both waking and sleeping retention. Classification performance in the "AM-PM-PM" condition decreased non-significantly across the day but improved significantly after sleep. Likewise, performance in the "PM-AM-PM" condition improved significantly after a night of sleep followed by a non-significant change across the next day. The results demonstrate that sleep produces a pattern of memory benefits in starlings that is similar to that observed in humans, providing clear behavioral evidence of sleep-dependent consolidation in an adult animal (Brawn et al. 2010a).

One intriguing difference between the patterns of results in the starling and human studies is that task performance in humans often deteriorates significantly across the day (e.g., Fenn et al. 2003, 2013; Ellenbogen et al. 2006, 2009; Brawn et al. 2008, 2010b; Payne et al. 2008), whereas the performance decline across waking retention was not significant in the starlings. Though species or task-related differences could explain this inconsistency, this difference could also reflect the negative effects of interference in humans because daytime behavior in human studies is rarely controlled. The starlings, however, were isolated throughout the experiments and were only presented with a very familiar baseline stimulus set when they were not participating in training or testing sessions, thus greatly reducing potential sources of interference. To address this possibility, we expanded the auditory classification paradigm to explore the interaction between interference and consolidation across waking and sleeping retention by training starlings on two similar classification tasks (Brawn et al. 2013).

In this study, starlings each completed 7 experimental conditions that followed an A–B–A (interference) or A–A (control) design. Training and testing, as before,

were accomplished using the Go/No-Go paradigm. In the wake-retention sessions, starlings were trained and tested on classification A in the morning and retested in the evening. Starlings were additionally trained on classification B, which consisted of a novel pair of starling song stimuli, immediately after completing task A ("Early Interference") or 4 h later ("Late Interference"). In the sleep-retention sessions, starlings were trained and tested on task A and retested after a night of sleep. Similar to the wake-retention sessions, starlings were trained and tested on task B after completing task A ("Early Interference"), 4 h later ("Late Interference"), or on the next morning prior to the post-retention test ("Post-sleep Interference"). Two control conditions were also run ("Wake" and "Sleep" Control), which did not include task B interference. The "Wake Control" condition exhibited a non-significant performance decline across the day (Fig. 4b). Classification performance for task A, however, deteriorated significantly across waking retention in the "Early Interference" and "Late Interference" conditions. In contrast, classification performance improved significantly after sleep for the "Sleep Control" and the sleep interference conditions ("Early," "Late," and "Post-Sleep"). This pattern of results indicates that learning a second classification task retroactively interfered with the memory of classification A, resulting in significantly impaired performance after waking retention. Nonetheless, sleep consolidated the memory of classification A such that performance was enhanced and stabilized after sleep to the point of eliminating any measurable effect of interference (Brawn et al. 2013).

Knowing the fate of the memory for classification A, we conducted an additional experiment to determine whether the interfering material (i.e., classification task B) was also consolidated across sleep. In this experiment, starlings each completed 6 conditions that followed an A–B–B (interference) or B–B (control) design in which they were retested on task B rather than task A after waking or sleeping retention. In the Early Interference conditions, starlings were trained on task A in the morning and then immediately trained on task B. The "Early Wake" condition was then retested on task B in the evening, and the "Early Sleep" condition was retested on the following day. In the Late Interference conditions, starlings were trained on task A in the morning and then trained on task B 4 h later. The "Late Wake" condition was then retested on task B in the evening and the "Late Sleep" condition was retested on task B on the following day. Two wake control conditions ("Early" and "Late" Control) were only trained and tested on task B at the same times as the Early and Late Interference conditions, respectively. Classification performance in the "Early Control" and "Late Control" conditions, as before, exhibited a non-significant decline across their respective waking retention intervals (Fig. 4c). In contrast, task B performance significantly deteriorated across the same intervals in the "Early Interference" and "Late Interference" wake conditions, demonstrating that the learning of classification A prior to classification B proactively interfered with the memory of classification B at the end of the day. Despite this proactive interference, classification performance on task B was significantly improved after sleep in both the "Early Interference" and "Late Interference" sleep conditions (Brawn et al. 2013).

Together, these two interference studies reveal that the learning of each classification reliably interfered, retroactively and proactively, with the retention of the

other classification across wakefulness. Sleep, however, consolidated the memories of both classifications even after performance was impaired by interference prior to sleep. Though interference increased the performance loss across waking retention, performance after sleep was no different in the interference and control conditions. Thus, as in the human studies of interference and sleep consolidation (e.g., Ellenbogen et al. 2006), the inclusion of the interfering material actually magnified the memory benefit of sleep. These observations demonstrate that sleep consolidation separately enhances memory of interfering experiences, facilitating opportunistic daytime learning. This system is ripe for further exploration: For example, "What types of memories interfere with each other?"; "Does the time course of performance loss or magnitude of interference depend on the complexity of the task?"; "Does the consolidated memory remain stable over many days?"; "Will the pattern of performance loss followed by post-sleep recovery be observed in other forms of associative memory formation?" and many others. Answers to these questions can help provide a rich behavioral framework for theory making as well as help to direct neurophysiological experiments designed to test those theories.

8 Toward a Behavioral Neuroscience of Auditory Sleep Consolidation in Starlings

The auditory classification learning experiments described above support the hypothesis that sleep benefits memory in starlings in a manner similar to that observed in humans. How sleep benefits memory in starlings is not yet known. Fortunately, we can take advantage of the well-studied songbird auditory system and the rich literature on mammalian sleep consolidation to guide future studies of sleep consolidation in starlings.

Songbirds have a well-developed circuitry underlying auditory perception. Auditory information is sent from cochlear nuclei in the brainstem to the mesencephalicus lateralis dorsalis, a midbrain structure akin to the mammalian inferior colliculus, and then to the nucleus ovoidalis (Ov) of the thalamus (Karten 1967). Different subdivisions of nucleus Ov project to different subdivisions of Field L (Karten 1968), an auditory forebrain structure that has homologies with mammalian primary auditory cortex. Field L is comprised of four or five highly interconnected subdivisions (Fortune and Margoliash 1992). Areas L2a and L2b receive the majority of thalamic input from the core region of Ov, whereas areas L1 and L3 receive some input from the shell region of Ov. The core and shell projections from Ov to Field L thus represent different functional pathways (Durand et al. 1992; Wild et al. 1993).

Traditionally, the avian auditory system has been viewed as having a hierarchical organization. Field L has unidirectional projections to the caudomedial nidopallium (NCM) and reciprocal connections with the caudolateral mesopallium (CLM). The caudomedial mesopallium (CMM), which in some accounts is the apex of the auditory hierarchy, contains reciprocal connections with both NCM and CLM yet

has no (substantial) direct connections with Field L (Vates et al. 1996). The neural response properties along the auditory pathway have been interpreted to reflect this hierarchical organization, with CMM exhibiting increased nonlinearity and selectivity for complex acoustic features compared to lower auditory areas (Müller and Leppelsack 1985; Sen et al. 2001; Theunissen et al. 2004; Meliza et al. 2010). However, this hierarchical conception of the avian auditory system is under active revision. Recent anatomical work in the auditory regions of chick brain slices identified radial patterns of organization with connections between CLM, CMM, and Field L that are evocative of the columnar organization and connectivity of mammalian neocortex (Wang et al. 2010). This revised conception identifies L3 as the output structure of the avian auditory cortex, with L3 neurons akin to neocortical layer 5/6 neurons. In support of this interpretation, a recent survey of the response properties across starling auditory cortex found L3 to have among the most selective responses of any structure as well as a broader and multipeaked distribution of neurons tolerant to within-class distinctions (Meliza and Margoliash 2012).

The response properties of the higher auditory areas CMM, CLM, and NCM express differential effects of learning (Thompson and Gentner 2010; Jeanne et al. 2011; Meliza and Margoliash 2012), suggesting these areas as likely contributing to physiological mechanisms that drive sleep consolidation of auditory classification learning in starlings. CMM appears particularly important for learning to categorize conspecific song. Training starlings to classify novel starling song using a Go/No-Go or Two-Alternative Choice task enhances the neural representation of the trained songs within CMM such that CMM neurons exhibit a significant preference for trained songs compared to novel songs. This enhanced response to trained songs was broadly represented across the population of CMM neurons. Moreover, CMM neurons prefer positively reinforced songs (Go stimuli) to negatively reinforced songs (No-Go stimuli) (Gentner and Margoliash 2003). These findings indicate that not only are CMM neurons responsive to the spectrotemporal characteristics of the stimulus but also to the behavioral saliency of the song.

Whereas the enhanced response of CMM neurons was observed in starlings as they reached asymptotic performance on the Go/No-Go or Two-Alternative Choice task (Gentner and Margoliash 2003), more recent work has investigated the response properties of CMM over the course of classification learning (D. Zaraza, unpublished results). This has provided a more nuanced view of the dynamics between CMM activity and the representation of the auditory classification memory. In this work, starlings were extensively trained on a Go/No-Go task to classify a pair of novel starlings' songs. Single units in CMM were recorded from starlings in an awake-restrained preparation at the conclusion of each daily training session after starlings had maintained at least 10 days of asymptotic performance on the classification task. In contrast to the results described above, the population response in CMM did not differ between the trained and unfamiliar songs, which suggests that the representation of familiar songs in CMM changes as the bird progresses from learning the auditory classification to being vastly over-trained. There was, however, a residual trace of responses to motifs of the trained songs. The starlings were then transferred to a novel pair of training songs, which resulted

in an increased response of CMM neurons to the new songs. Remarkably, learning the new songs reactivated the representation of the old training songs such that the CMM population again expressed an enhanced response to the old training songs. The strength and selectivity of CMM responses to both the new and old songs diminished as classification performance on the new songs improved to asymptotic levels, with responses to the new songs maintained in the same manner of a bias of responses to the familiar motifs.

NCM, which is reciprocally connected to CMM, is also involved in starling song recognition behavior, albeit in the opposite direction of CMM. Training starlings to classify conspecific songs induces a stimulus specific weakening of the neural responses of individual NCM neurons even as the population continues to respond to unfamiliar songs (Thompson and Gentner 2010). Recent work surveying neural selectivity across avian auditory cortex has confirmed the opposing functions of CMM and NCM, with distinctions (differences in response) to familiar songs being represented in CMM and unfamiliarity being represented in NCM (Meliza and Margoliash 2012). Studies of stimulus-driven expression of the immediate early gene Zenk further support the functional distinction between CMM and NCM in song recognition behavior. Expression of Zenk in NCM was only elevated in starlings trained to classify novel songs compared to starlings that continued to classify familiar songs or that heard no song. In contrast, Zenk expression was enhanced in CMM of starlings that continued to classify familiar songs or that learned to classify novel songs compared to control starlings that heard no song (Gentner et al. 2004).

The identification of CMM and NCM as important to song recognition and classification coupled with the clear sleep-dependent improvements in song classification memory suggest these areas as a potential source of activity underlying sleep-dependent consolidation of auditory classification memory in starlings. Future studies that incorporate neural recordings from these areas in conjunction with the auditory classification sleep paradigm will test how the response properties of these populations change across sleep. One hypothesis is that the population response strength and selectivity of CMM to newly trained songs will increase as a result of post-training sleep. This is suggested by the behavioral evidence of memory improvements after sleep (Brawn et al. 2010a, 2013) in conjunction with results showing a significant correlation between changes in CMM activity and classification performance during the learning of auditory classifications (D. Zaraza, unpublished data). In contrast, since the classification memory of the newly trained stimuli is better, and therefore more familiar, after sleep, it is hypothesized that the population response to the trained stimuli in NCM will become weaker during sleep.

Though we do not yet know how sleep benefits auditory classification memory in starlings, neural reactivation during sleep seems plausible given that replay has been identified in zebra finches (Dave and Margoliash 2000), albeit in motor rather than auditory regions. Though the function of sleep reactivations, even in established cases, is not yet clear, it may act as a form of offline rehearsal to strengthen synapses involved in a recently acquired memory or as a mechanism to transfer the memory

from a temporary to long-term storage. It is not known whether the long-term song classification memory resides in CMM or elsewhere. The rapid enhancement of CMM responses to trained versus unfamiliar songs followed by a relaxation of those responses indicates that the memory could reside in CMM in a more efficient form or could be transferred out of CMM to a different long-term store. Overall, investigations to connect the underlying mechanisms of sleep-dependent consolidation to the behavioral benefits of sleep in starlings are just beginning. The comparable behavioral patterns of memory consolidation observed in humans and starlings combined with an increasing recognition of similar sleep patterns and brain organization between avian and mammalian species give confidence that auditory classification learning in starlings will continue to develop into a productive animal model of sleep-dependent memory consolidation.

9 Conclusion

Throughout this chapter, we have presented a comparative perspective on the current state of sleep-dependent memory consolidation and have highlighted how the study of sleep and memory in birds has contributed to and advanced this understanding. A key point we emphasize is the necessity of incorporating behavioral measures of memory within mechanistic studies of sleep consolidation. To date, human studies have largely consisted of behavioral demonstrations of a growing list of different memory tasks that are consolidated by sleep. In some cases, imaging and polysomnography have additionally determined brain regions and sleep states involved in the sleep consolidation. In contrast, animal studies have described potential neural mechanisms of sleep consolidation but often without showing that the animal's memory benefited from the proposed mechanisms. Or, in the case of sensorimotor vocal learning, the effects are complex in animals and yet to be related to similar effects in humans.

Fortunately, both human and animal studies are progressing toward bridging the gap between brain and behavior. For example, recent behavioral experiments in humans have manipulated brain oscillations during sleep via transcranial magnetic (Marshall et al. 2006) or auditory (Ngo et al. 2013) stimulation and have attempted to reactivate recently acquired memories via olfactory (Diekelmann et al. 2011) or auditory (Rudoy et al. 2009; Antony et al. 2012) cues. Likewise, recent studies of neural reactivation in rats have incorporated pre- and post-sleep behavioral measures of spatial tasks (Girardeau et al. 2009; Ego-Stengel and Wilson 2010). Our work in birds also represents an attempt to bring together brain and behavior in the study of sleep consolidation. In zebra finches, we have profited from the substantial literature on the behavior and neural mechanisms of birdsong learning and production in an attempt to relate neural activity during sleep to the learning and maintenance of song. In starlings, we have taken advantage of the importance of song recognition behavior and developed an auditory classification task that has demonstrated that starlings express sleep-dependent memory benefits in a manner

similar to that observed in humans. Though the physiological analysis of sleep in relation to auditory classification learning is just beginning, future studies will be guided by the extensive knowledge of how song is represented within the avian auditory cortex.

Given the universality of sleep within the animal kingdom, there may be a general function of sleep that applies broadly across species. Yet, it is also plausible that sleep will have distinct effects in different species, in different physiological systems, and on different behaviors. Evaluating the function of sleep through the behavioral specializations of different species will only help to broaden our understanding of sleep. Our work in songbirds exploring how sleep is involved in the learning, maintenance, and recognition of song represents one path toward that goal.

References

Aamodt SM, Nordeen EJ, Nordeen KW (1996) Blockade of NMDA receptors during song model exposure impairs song development in juvenile zebra finches. Neurobiol Learn Mem 65:91–98

Abel M, Bäuml KH (2013) Sleep can reduce proactive interference. Memory:1–8

Adret P (2004) In search of the song template. Ann N Y Acad Sci 1016:303–324

Adret P, Meliza CD, Margoliash D (2012) Song tutoring in presinging zebra finch juveniles biases a small population of higher-order song-selective neurons toward the tutor song. J Neurophysiol 108:1977–1987

Adret-Hausberger M, Jenkins P (1988) Complex organization of the warbling song in the European starling Sturnus vulgaris. Behaviour 107:138–156

Alger SE, Lau H, Fishbein W (2012) Slow wave sleep during a daytime nap is necessary for protection from subsequent interference and long-term retention. Neurobiol Learn Mem 98:188–196

Alvarez-Buylla A, Theelen M, Nottebohm F (1988) Birth of projection neurons in the higher vocal center of the canary forebrain before, during, and after song learning. Proc Nat Acad Sci USA 85:8722–8726

Amlaner CJ, Ball NJ (1994) Avian sleep. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 2nd edn. W.B. Saunders, Philadelphia, pp 81–94

Andalman AS, Fee MS (2009) A basal ganglia-forebrain circuit in the songbird biases motor output to avoid vocal errors. Proc Nat Acad Sci USA 106:12518–12523

Antony JW, Gobel EW, O'Hare JK et al (2012) Cued memory reactivation during sleep influences skill learning. Nature 15:1114–1116

Aronov D, Andalman AS, Fee MS (2008) A specialized forebrain circuit for vocal babbling in the juvenile songbird. Science 320:630–634

Ayala-Guerrero F, Perez MC, Calderon A (1988) Sleep patterns in the bird Aratinga canicularis. Physiol Behav 43:585–589

Ayala-Guerrero F (1989) Sleep patterns in the parakeet Melopsittacus undulatus. Physiol Behav 46:787–791

Ball GF, Balthazart J (2010) Introduction to the chemical neuroanatomy of birdsong. J Chem Neuroanat 39:67–71

Belgard TG, Montiel JF (2013) Things change: how comparative transcriptomics suggest the pallium has evolved at multiple levels of organization. Brain Behav Evol 82:150–152

Belgard TG, Montiel JF, Wang WZ, Garcia-Moreno F, Margulies EH, Ponting CP, Molnar Z (2013) Adult pallium transcriptomes surprise in not reflecting predicted homologies across diverse chicken and mouse pallial sectors. Proc Nat Acad Sci USA 110:13150–13155

Bendor D, Wilson M (2012) Biasing the content of hippocampal replay during sleep. Nat Neurosci 15:1439–1444
Binder S, Baier PC, Molle M, Inostroza M, Born J, Marshall L (2012) Sleep enhances memory consolidation in the hippocampus-dependent object-place recognition task in rats. Neurobiol Learn Mem 97:213–219
Brainard MS, Doupe AJ (2000) Auditory feedback in learning and maintenance of vocal behaviour. Nat Rev Neurosci 1:31–40
Brawn TP, Fenn KM, Nusbaum HC, Margoliash D (2008) Consolidation of sensorimotor learning during sleep. Learning and Memory 15:815–819
Brawn TP, Nusbaum HC, Margoliash D (2010a) Sleep-dependent consolidation of auditory discrimination learning in adult starlings. J Neurosci 30:609–613
Brawn TP, Fenn KM, Nusbaum HC, Margoliash D (2010b) Consolidating the effects of waking and sleep on motor-sequence learning. J Neurosci 30:13977–13982
Brawn TP, Nusbaum HC, Margoliash D (2013) Sleep consolidation of interfering auditory memories in starlings. Psychol Sci 24:439–447
Cai DJ, Shuman T, Gorman MR, Sage JR, Anagnostaras SG (2009) Sleep selectively enhances hippocampus-dependent memory in mice. Behav Neurosci 123:713–719
Campbell SS, Tobler I (1984) Animal sleep: A review of sleep duration across phylogeny. Neurosci Biobehav Rev 8:269–300
Carrillo GD, Doupe AJ (2004) Is the songbird Area X striatal, pallidal, or both? An anatomical study. J Comp Neurol 473:415–437
Cirelli C, Tononi G (2008) Is sleep essential. PLoS Biology 6(8):e216
Dave AS, Margoliash D (2000) Song replay during sleep and computational rules for sensorimotor vocal learning. Science 290:812–816
Derégnaucourt S, Mitra PP, Fehér O et al (2005) How sleep affects the developmental learning of bird song. Nature 433:710–716
Diekelmann S, Born J (2010) The memory function of sleep. Nature Reviews Neuroscience: 1–13
Diekelmann S, Büchel C, Born J, Rasch B (2011) Labile or stable: opposing consequences for memory when reactivated during waking and sleep. Nature:1–8
Dragoi G, Tonegawa S (2011) Preplay of future place cell sequences by hippocampal cellular assemblies. Nature 469:397–401
Dragoi G, Tonegawa S (2013) Distinct preplay of multiple novel spatial experiences in the rat. Proc Nat Acad Sci USA 110:9100–9105
Drosopoulos S, Schulze C, Fischer S, Born J (2007) Sleep's function in the spontaneous recovery and consolidation of memories. J Exp Psychol Gen 136:169–183
Dugas-Ford J, Rowell JJ, Ragsdale CW (2012) Cell-type homologies and the origins of the neocortex. Proc Nat Acad Sci USA 109:16974–16979
Durand SE, Tepper JM, Cheng MF (1992) The shell region of the nucleus ovoidalis: a subdivision of the avian auditory thalamus. J Comp Neurol 323(4):495–518
Eens M (1997) Understanding the complex song of the European starling: an integrated ethological approach. Adv Study Behav 26:355–434
Ego-Stengel V, Wilson MA (2010) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20:1–10
Ellenbogen JM, Hu PT, Payne JD et al (2007) Human relational memory requires time and sleep. Proc Nat Acad Sci USA 104:7723–7728
Ellenbogen JM, Hulbert JC, Jiang Y, Stickgold R (2009) The sleeping brain's influence on verbal memory: boosting resistance to interference. PLoS ONE 4:e4117
Ellenbogen JM, Hulbert JC, Stickgold R et al (2006) Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. Curr Biol 16:1290–1294
Eschenko O, Molle M, Born J, Sara SJ (2006) Elevated sleep spindle density after learning or after retrieval in rats. J Neurosci 26:12914–12920
Eschenko O, Ramadan W, Molle M et al (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 15:222–228

Euston DR, Tatsuno M, McNaughton BL (2007) Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. Science 318:1147–1150
Farries MA, Ding L, Perkel DJ (2005) Evidence for direct and indirect pathways through the song system basal ganglia. J Comp Neurol 484:93–104
Farries MA, Perkel DJ (2002) A telencephalic nucleus essential for song learning contains neurons with physiological characteristics of both striatum and globus pallidus. J Neurosci 22:3776–3787
Fenn KM, Margoliash D, Nusbaum HC (2013) Sleep restores loss of generalized but not rote learning of synthetic speech. Cognition 128:280–286
Fenn KM, Nusbaum HC, Margoliash D (2003) Consolidation during sleep of perceptual learning of spoken language. Nature 425:614–616
Ferrara M, Iaria G, Tempesta D et al (2008) Sleep to find your way: the role of sleep in the consolidation of memory for navigation in humans. Hippocampus 18:844–851
Finger TE, Yamamoto N, Karten HJ, Hof PR (2013) Evolution of the forebrain—revisiting the pallium. J Comp Neurol 521:3601–3603
Fischer S, Nitschke MF, Melchert UH et al (2005) Motor memory consolidation in sleep shapes more effective neuronal representations. J Neurosci 25:11248–11255
Fortune ES, Margoliash D (1992) Cytoarchitectonic organization and morphology of cells of the field L complex in male zebra finches (Taenopygia guttata). J Comp Neurol 325:388–404
Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6:119–130
Gais S, Lucas B, Born J (2006) Sleep after learning aids memory recall. Learning and Memory 13:259–262
Gais S, Plihal W, Wagner U, Born J (2000) Early sleep triggers memory for early visual discrimination skills. Nat Neurosci 3:1335–1339
Gentner TQ, Hulse SH (2000) Perceptual classification based on the component structure of song in European starlings. J Acoust Soc Am 107:3369–3381
Gentner TQ, Hulse SH, Ball GF (2004) Functional differences in forebrain auditory regions during learned vocal recognition in songbirds. J Comp Physiol A 190:1001–1010
Gentner TQ, Hulse SH, Bentley GE, Ball GF (2000) Individual vocal recognition and the effect of partial lesions to HVc on discrimination, learning, and categorization of conspecific song in adult songbirds. J Neurobiol 42:117–133
Gentner TQ, Margoliash D (2003) Neuronal populations and single cells representing learned auditory objects. Nature 424:669–674
Girardeau G, Benchenane K, Wiener SI et al (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nature 12:1222–1223
Gobes SMH, Zandbergen MA, Bolhuis JJ (2010) Memory in the making: Localized brain activation related to song learning in young songbirds. Proc R Soc B 277:3343–3351
Goldman SA, Nottebohm F (1983) Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain. Proc Nat Acad Sci USA 80:2390–2394
Gomez RL, Bootzin RR, Nadel L (2006) Naps promote abstraction in language-learning infants. Psychol Sci 17:670–674
Graves LA, Heller EA, Pack AI, Abel T (2003) Sleep deprivation selectively impairs memory consolidation for contexual fear conditioning. Learn Mem 10:168–176
Hackett SJ, Kimball RT, Reddy S et al (2008) A phylogenomic study of birds reveals their evolutionary history. Science 320:1763–1768
Hagewoud R, Whitcomb SN, Heeringa AN, Havekes R, Koolhaas JM, Meerlo P (2010) A time for learning and a time for sleep: the effect of sleep deprivation on contextual fear conditioning at different times of the day. Sleep 330:1315–1322
Horn G, Nicol AU, Brown MW (2001) Tracking memory's trace. Proc Nat Acad Sci USA 98:5282–5287
Hotermans C, Peigneux P, Maertens de Noordhout A et al (2006) Early boost and slow consolidation in motor skill learning. Learn Mem 13:580–583

Hu P, Stylos-Allan M, Walker MP (2006) Sleep facilitates consolidation of emotional declarative memory. Psychol Sci 17:891–898
Hupbach A, Gomez RL, Bootzin RR, Nadel L (2009) Nap-dependent learning in infants. Develop Sci 12:1007–1012
Inostroza M, Binder S, Born J (2013) Sleep-dependency of episodic-like memory consolidation in rats. Behav Brain Res 237:15–22
Jackson C, McCabe BJ, Nicol AU, Grout AS, Brown MW, Horn G (2008) Dynamics of a memory trace: effects of sleep on consolidation. Curr Biol 18:393–400
Jarvis ED, Güntürkün O, Bruce L et al (2005) Avian brains and a new understanding of vertebrate brain evolution. Nat Rev Neurosci 6:151–159
Jeanne JM, Thompson JV, Sharpee TO, Gentner TQ (2011) Emergence of learned categorical representations within an auditory forebrain circuit. J Neurosci 31:2595–2606
Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10:100–107
Jones SG, Vyazovskiy VV, Cirelli C et al (2008) Homeostatic regulation of sleep in the white-crowned sparrow (Zonotrichia leucophrys gambelii). BMC Neuroscience 9:47
Kao MH, Doupe AJ, Brainard MS (2005) Contributions of an avian basal ganglia-forebrain circuit to real-time modulation of song. Nature 433:638–643
Karten HJ (1967) The organization of the ascending auditory pathway in the pigeon (*Columbia livia*). I. Diencephalic projections of the inferior colliculus (nucleus mesencephali lateralis, pars dorsalis. Brain Res 6:409–427
Karten HJ (1968) The ascending auditory pathway in the pigeon (*Columbia livia*). II. Telencephalic projections of the nucleus ovoidalis thalami. Brain Res 11:134–153
Karten HJ (1997) Evolutionary developmental biology meets the brain: the origins of mammalian cortex. Proc Nat Acad Sci USA 94:2800–2804
Kempler L, Richmond JL (2012) Effect of sleep on gross motor memory. Memory:1–8
Korman M, Doyon J, Doljansky J et al (2007) Daytime sleep condenses the time course of motor memory consolidation. Nat Neurosci 10:1206–1213
Korman M, Raz N, Flash T, Karni A (2003) Multiple shifts in the representation of a motor sequence during the acquisition of skilled performance. Proc Nat Acad Sci USA 100:12492–12497
Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19:4090–4101
Kuriyama K, Stickgold R, Walker MP (2004) Sleep-dependent learning and motor-skill complexity. Learn Mem 11:705–713
Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36:1183–1194
Lesku JA, Roth TC 2nd, Rattenborg NC, Amlaner CJ, Lima SL (2009) History and future of comparative analyses in sleep research. Neurosci Biobehav Rev 33:1024–1036
Lipkind D, Tchernichovski O (2011) Quantification of developmental birdsong learning from the subsyllabic scale to cultural evolution. Proc Nat Acad Sci USA 108:15572–15579
London SE, Clayton DF (2008) Functional identification of sensory mechanisms required for developmental song learning. Nat Neurosci 11:579–586
Low PS, Shank SS, Sejnowski TJ, Margoliash D (2008) Mammalian-like features of sleep structure in zebra finches. Proc Nat Acad Sci USA 105:9081–9086
Marler P (1997) Three models of song learning: evidence from behavior. J Neurobiol 33:501–516
Margoliash D (2002) Evaluating theories of bird song learning: implications for future directions. J Comp Physiol A 188:851–866
Marshall L, Born J (2007) The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci 11:442–450
Marshall L, Helgadóttir H, Mölle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613

Martinez-Gonzalez D, Lesku JA, Rattenborg NC (2008) Increased EEG spectral power density during sleep following short-term sleep deprivation in pigeons (Columba livia): evidence for avian sleep homeostasis. J Sleep Res 17:140–153
Mednick SC, Nakayama K, Cantero JL et al (2002) The restorative effect of naps on perceptual deterioration. Nat Neurosci 5:677–681
Mednick S, Nakayama K, Stickgold R (2003) Sleep-dependent learning: a nap is as good as a night. Nat Neurosci 6:697–698
Mednick SC, Arman AC, Boynton GM (2005) The time course and specificity of perceptual deterioration. Proc Nat Acad Sci USA 102:3881–3885
Meliza CD, Chi Z, Margoliash D (2010) Representations of conspecific song by starling secondary forebrain auditory neurons: toward a hierarchical framework. J Neurophysiol 103:1195–1208
Meliza CD, Margoliash D (2012) Emergence of selectivity and tolerance in the avian auditory cortex. J Neurosci 32:15158–15168
Montiel JF, Molnar Z (2013) The impact of gene expression analysis on evolving views of avian brain organization. J Comp Neurol 521:3604–3613
Müller CM, Leppelsack HJ (1985) Feature extraction and tonotopic organization in the avian auditory forebrain. Exp Brain Res 59:587–599
Ngo H-VV, Martinetz T, Born J, Mölle M (2013) Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 78:545–553
Nishida M, Walker MP (2007) Daytime naps, motor memory consolidation and regionally specific sleep spindles. PLoS ONE 2:e341
Nordeen KW, Nordeen EJ (1992) Auditory feedback is necessary for the maintenance of stereotyped song in adult zebra finches. Behav Neural Biol 57:58–66
Ölveczky BP, Andalman AS, Fee MS (2005) Vocal experimentation in the juvenile songbird requires a basal ganglia circuit. PLoS Biol 3:e153
O'Neill J, Pleydell-Bouverie B, Dupret D, Csicsvari J (2010) Play it again: reactivation of waking experience and memory. Trends Neurosci 33:220–229
Paton JA, Nottebohm F (1984) Neurons born in adult brain are recruited into functional circuits. Science 225:1046–1048
Paus M, Kiefmann M, Churakov G et al (2011) ncomms1448. Nat Commun 2:443–447. doi:10.1038/ncomms1448
Payne JD (2011) Learning, memory, and sleep in humans. Clin Sleep Med 6:15–30
Payne JD, Stickgold R, Swanberg K, Kensinger EA (2008) Sleep preferentially enhances memory for emotional components of scenes. Psychol Sci 19:781–788
Peyrache A, Khamassi M, Benchenane K et al (2009) Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nature 12:919–926
Ramadan W, Eschenko O, Sara SJ (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. PLoS ONE 4:e6697
Rasch B, Born J (2013) About sleep's role in memory. Physiol Rev 93:681–766
Rasch B, Born J (2007) Maintaining memories by reactivation. Curr Opin Neurobiol 17:698–703
Rattenborg NC, Amlaner CJ, Lima SL (2000) Behavioral, neurophysiological and evolutionary perspectives on unihemispheric sleep. Neurosci Biobehav Rev 24:817–842
Rattenborg NC, Amlaner CJ (2010) A bird's-eye view of the function of sleep. In: McNamara P, Barton RA, Nunn CL (eds) Evolution of Sleep. Cambridge University Press, Cambridge, pp 145–171
Rattenborg NC, Martinez-Gonzalez D, Lesku JA (2009) Avian sleep homeostasis: Convergent evolution of complex brains, cognition and sleep functions in mammals and birds. Neurosci Biobehav Rev 33:253–270
Rattenborg NC, Martinez-Gonzalez D, Roth TC II, Pravosudov VV (2011) Hippocampal memory consolidation during sleep: a comparison of mammals and birds. Biol Rev Camb Philos Soc 86:658–691
Rauske PL, Chi Z, Dave AS, Margoliash D (2010) Neuronal stability and drift across periods of sleep: Premotor activity patterns in a vocal control nucleus of adult zebra finches. J Neurosci 30:2783–2794

Reiner A, Perkel DJ, Bruce LL et al (2004a) Revised nomenclature for avian telencephalon and some related brainstem nuclei. J Comp Neurol 473:377–414
Reiner A, Perkel DJ, Mello CV, Jarvis ED (2004b) Songbirds and the revised avian brain nomenclature. Ann NY Acad Sci 1016:77–108
Reiner A, Yamamoto K, Karten HJ (2005) Organization and evolution of the avian forebrain. Anat Rec A 287:1080–1102
Rickard TC, Cai DJ, Rieth CA et al (2008) Sleep does not enhance motor sequence learning. J Exp Psychol Learn Mem Cogn 34:834–842
Rieth CA, Cai DJ, McDevitt EA, Mednick SC (2010) The role of sleep and practice in implicit and explicit motor learning. Behav Brain Res 214:470–474
Robertson EM, Pascual-Leone A, Press DZ (2004) Awareness Modifies the Skill-Learning Benefits of Sleep. Curr Biol 14:208–212
Rudoy JD, Voss JL, Westerberg CE, Paller KA (2009) Strengthening individual memories by reactivating them during sleep. Science 326:1079
Scharff C, Nottebohm F (1991) A comparative study of the behavioral deficits following lesions of various parts of the zebra finch song system: implications for vocal learning. J Neurosci 11:2896–2913
Schmidt DF, Ball NJ, Amlaner CJ (1990) The characteristics and quantities of sleep in the Aebra finch (*genus Taenopygia*). Sleep Res 14:103
Scullin MK, McDaniel MA (2010) Remembering to execute a goal: sleep on it! Psychol Sci 21:1028–1035
Sen K, Theunissen FE, Doupe AJ (2001) Feature analysis of natural sounds in the songbird auditory forebrain. J Neurophysiol 86:1445–1458
Shank SS, Margoliash D (2009) Sleep and sensorimotor integration during early vocal learning in a songbird. Nature 457:73–77
Sheth BR, Varghese R, Truong T (2012) Sleep shelters verbal memory from different kinds of interference. Sleep 35:985–996
Siegel JM (2008) Do all animals sleep? Trends Neurosci 31:208–213
Sohrabji F, Nordeen EJ, Nordeen KW (1990) Selective impairment of song learning following lesions of a forebrain nucleus in the juvenile zebra finch. Behav Neural Biol 53:51–63
Solis MM, Doupe AJ (1999) Contributions of tutor and bird's own song experience to neural selectivity in the songbird anterior forebrain. J Neurosci 19:4559–4584
Stickgold R, James L, Hobson JA (2000) Visual discrimination learning requires sleep after training. Nat Neurosci 3:1237–1238
Szymcazk JT (1985) Sleep pattern in the starling (Sturnus vulgaris). Acta Physiol Pol 36:323–331
Szymcazk JT (1986) Daily rhythm of sleep-wakefulness in the starling, Sturnus vulgaris. Acta Physiol Pol 37:199–206
Talamini LM, Nieuwenhuis ILC, Takashima A, Jensen O (2008) Sleep directly following learning benefits consolidation of spatial associative memory. Learn Mem 15:233–237
Tchernichovski O, Lints TJ, Deregnaucourt S et al (2004) Studying the song development process: Rationale and methods. Ann NY Acad Sci 1016:348–363
Tchernichovski O, Mitra PP, Lints T, Nottebohm F (2001) Dynamics of the vocal imitation process: how a zebra finch learns its song. Science 291:2564–2569
Terpstra NJ, Bolhuis JJ, Riebel K et al (2005) Localized brain activation specific to auditory memory in a female songbird. J Comp Neurol 494:784–791
Theunissen FE, Amin N, Shaevitz SS et al (2004) Song selectivity in the song system and in the auditory forebrain. Ann NY Acad Sci 1016:222–245
Thompson JV, Gentner TQ (2010) Song recognition learning and stimulus-specific weakening of neural responses in the avian auditory forebrain. J Neurophysiol 103:1785–1797
Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
Tucker M, Hirota Y, Wamsley E et al (2006) A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem 86:241–247

Vates GE, Broome BM, Mello CV, Nottebohm F (1996) Auditory pathways of caudal telencephalon and their relation to the song system of adult male zebra finches. J Comp Neurol 366:613–642

Walker MP (2005) A refined model of sleep and the time course of memory formation. Behav Brain Sci 28:51–64

Walker MP, Brakefield T, Morgan A et al (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211

Walker MP, Brakefield T, Hobson JA, Stickgold R (2003) Dissociable stages of human memory consolidation and reconsolidation. Nature 425:616–620

Walker MP, Stickgold R (2006) Sleep, memory, and plasticity. Ann Rev Psychol 57:139–166

Wang Y, Brzozowska-Prechtl A, Karten HJ (2010) Laminar and columnar auditory cortex in avian brain. Proc Nat Acad Sci USA 107:12676–12681

Wild JM, Karten HJ, Frost BJ (1993) Connections of the auditory forebrain in the pigeon (Columba livia). J Comp Neurol 337:32–62

Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–679

Yu AC, Margoliash D (1996) Temporal hierarchical control of singing in birds. Science 273:1871–1875

Neuroimaging Studies of Sleep and Memory in Humans

Philippe Peigneux

Abstract Human brain dynamics are nowadays routinely explored at the macroscopic level using a wide variety of non-invasive neuroimaging techniques, including single photon emission computed tomography (SPECT) and positron emission tomography (PET), near infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI). In the past decades, the application of brain imaging methods to the study of sleep raised a renewed interest for the field, especially in the domain of neuroscience. Indeed, these studies enabled researchers to characterize the functional neuroanatomy of sleep stages and identify the neural correlates of phasic and tonic sleep mechanisms. Furthermore, they provided the scientific community with tools to address the crucial question of brain plasticity processes during human sleep, the role of sleep-related plasticity for memory consolidation, and how sleep and the lack of post-training sleep impacts brain functioning in the neural networks underlying memory-related cognitive processes. This chapter reviews the contributions of neuroimaging to our understanding of the functional neuroanatomy of sleep and sleep stages, and discusses how sleep contributes to the long-term consolidation of recently acquired memories in light of contemporary neural models for memory consolidation during sleep.

Keywords Sleep · Memory · Neuroimaging · Human · Sleep deprivation · Learning · Memory consolidation · Brain plasticity · Behaviour · Function of sleep · REM · NREM · SWS

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Contents

1 Functional Neuroanatomy of Sleep and Sleep Stages

Early positron emission tomography (PET) sleep studies were mostly conducted using the [18F]-fluorodeoxyglucose (FDG) tracer, now widely used in clinical settings. These studies revealed a striking diminution of global cerebral glucose metabolism during non-rapid eye movement (NREM) sleep (Buchsbaum et al. 1989; Maquet et al. 1990), especially during the slow wave sleep (SWS) phase (Maquet et al. 1990). Global cerebral glucose metabolism showed only small decreases during the light stage 2 of NREM sleep (Maquet et al. 1992), and most importantly was shown *not* to differ from wakefulness during the rapid eye movement (REM) sleep phase (Buchsbaum et al. 1989; Maquet et al. 1990). At the regional, local cerebral level, glucose consumption was shown to decrease in the thalamus during SWS (Buchsbaum et al. 1989; Maquet et al. 1990, 1992). However, the use of FDG whose radioactivity decays in the scale of hours does not allow repeated measurements within a same night, is not temporally precise enough to focus on one sleep stage in particular and is lacking power for an

accurate description of the brain areas involved in the mechanisms subtending the promotion and the maintenance of sleep. Hence, although the FDG-PET technique remains in use for the investigation of the neuroanatomy of some sleep-related disorders (for reviews see e.g. Maquet 2005; Nofzinger 2004; Desseilles et al. 2011) and even normal sleep (e.g. Buchsbaum et al. 2001; Nofzinger et al. 1997), inferences that can be drawn from these studies are constrained by technical limitations. One advantage, however, of the long half-life ($\sim$120 min) of this compound is that it allows for the injection of the tracer while the participant is still lying in his own bed during a sleep episode of interest, and the subject can be transferred to the scanner for acquisition at some time later, thus minimizing discomfort and allowing for longer periods of sleep (e.g. Nofzinger et al. 1998). Similar advantages and limitations apply to the single photon emission computed tomography (SPECT) technique, which was used to demonstrate sleep-related cerebral activity patterns associated with sleep disorders behaviours. For instance, this approach revealed a dissociation between the activation of thalamocingulate pathways and the persisting deactivation of other thalamocortical arousal systems during sleepwalking (Bassetti et al. 2000), or increased perfusion in the supplementary motor area during a REM sleep behaviour attack (Dauvilliers et al. 2011).

1.1 Non-Rapid Eye Movement Sleep

Further improvements in high-resolution PET scanners, the introduction of iterative regional cerebral blood flow (rCBF) measurements (especially using the $H_2{}^{15}O$ infusion technique) and the development of more powerful statistical methods have been critical determinants to allow a reliable delineation of the functional neuroanatomy of normal sleep stages in humans (for a critical methodological discussion, see Maquet 2000). Using the $H_2{}^{15}O$ technique, several studies (Andersson et al. 1998; Braun et al. 1997; Hofle et al. 1997; Kajimura et al. 1999; Maquet et al. 1997) showed that those areas in which cerebral blood flow (CBF) significantly decreases during SWS as compared to wakefulness and REM sleep are located in a distributed cerebral network including the dorsal pons and mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain/hypothalamus, prefrontal cortex, anterior cingulate cortex, precuneus and the mesial temporal lobe. At the time scale of PET recordings, averaging neural activity over tens of seconds, the alternation of short bursts of synchronized neuronal activity with "silent" periods dominated by hyperpolarization during SWS (Steriade and Amzica 1998) actually results in a net decrease in the metabolic rate and consequently in regional CBF (Maquet 2000). Accordingly, EEG spectral power in the 0.5–4 Hz range during NREM sleep negatively correlates with rCBF in those brain areas in which CBF decreases during SWS (Fig. 1), including in the ventromedial prefrontal cortex, the basal forebrain, the striatum, the anterior insula and the precuneus (Dang-Vu et al. 2005). No correlation with thalamic activity was found in this latter study however, in contrast to a prior PET study where waking and

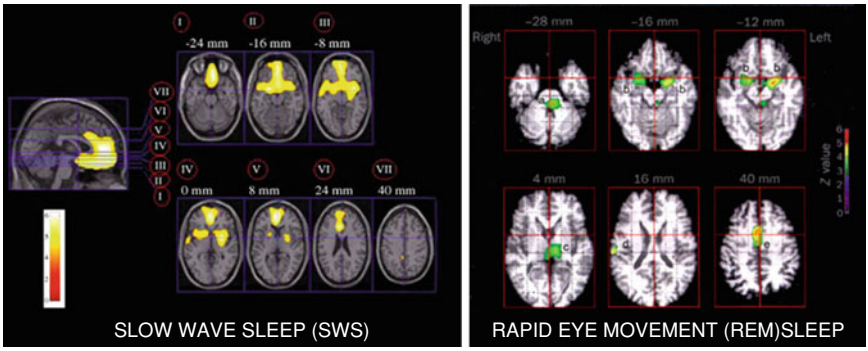

Fig. 1 Functional neuroanatomy of SWS and REM sleep. Brain sections showing brain areas where regional cerebral blood flow (rCBF) was negatively correlated with the density of slow oscillations (delta power) during SWS (*left panel*) or increased during REM sleep as compared to wakefulness (*right panel*). Adapted with permission from Dang-Vu et al. (2005) and Maquet et al. (1996)

NREM sleep scans were intermixed (Hofle et al. 1997). Hence the findings of Dang-Vu et al. (2005) support the proposal that extra-thalamic delta rhythms contribute to synchronous NREM sleep oscillations (Steriade 2003).

1.2 Rapid Eye Movements Sleep

In contrast to NREM sleep, REM sleep and wakefulness are characterized by sustained, desynchronized neuronal activity (Steriade and McCarley 1990) associated with high energy demands. Therefore, activity as measured using PET should be increased in brain regions actively involved in REM sleep as compared to NREM sleep, even above activity levels observed during wakefulness. Accordingly, regional patterns of activation have been observed during REM sleep using $H_2{}^{15}O$-PET (Braun et al. 1997; Maquet et al. 1996). These studies evidenced markedly increased rCBF in the mesopontine tegmentum, the thalamic nuclei, limbic (amygdaloid complexes, hippocampal formation, anterior cingulate cortex) and temporo-occipital areas (Fig. 1). Conversely, activity in the dorso-lateral prefrontal cortex, parietal cortex, as well as the posterior cingulate cortex and precuneus was reduced as compared to the awake resting-state. These results confirmed animal reports (e.g. Lydic et al. 1991) suggesting a heterogeneous and regionally specific distribution of telencephalic activity during REM sleep. Additionally, temporal correlations between neural activity in the amygdala and neuronal activity in the occipito-temporal areas during REM sleep suggested a modulation of these cortical areas by the limbic system (Maquet and Phillips 1998), which might participate in the mechanisms underlying dreaming activity (Schwartz and Maquet 2002) and emotional memory processing. $H_2{}^{15}O$ PET results also supported the hypothesis of the existence of ponto-geniculo-occipital

(PGO) waves in human (Peigneux et al. 2001). As evidenced in animal studies, PGO waves are responsible for the generation of REMs, and trigger cellular processes thought to favour brain plasticity during REM sleep (Datta 1999).

2 Transient and Oscillatory Processes in Sleep

Beyond regional patterns of sustained cerebral activity as evidenced by PET, functional magnetic resonance imaging (fMRI) has become a powerful tool for the description of the functional neuroanatomy of transient and oscillatory processes in sleep. fMRI, which records cerebral activity at the scale of the second, provides a more accurate temporal resolution than PET together with a good localizing power in the whole brain. A main disadvantage is the subject's discomfort in the scanner, due to elevated noise levels and the restricted space within the magnet. Nowadays, technical difficulties to get suitable EEG signal needed for the identification of sleep stages and characterization of sleep events in the fMRI environment are no longer an obstacle to research.

2.1 Stimulating the Brain to Understand the Neurophysiology of Sleep

Functional MRI studies initially focused on the cerebral correlates of auditory stimulations as a probe for the investigation of sleep neuroanatomy (Czisch et al. 2002, 2004; Kaufmann et al. 2006; Portas et al. 2000; Wehrle et al. 2007). The choice of auditory stimulations in sleep was mostly for practical and technical reasons, as it is rather easy to deliver sounds at non-awakening threshold in the context of the magnetic environment, as compared to e.g. tactile stimulations. Results of these studies mostly confirmed PET findings in terms of sleep stage-specific (Czisch et al. 2002, 2004; Kaufmann et al. 2006; Portas et al. 2000; Wehrle et al. 2007) and PGO-related (Kaufmann et al. 2006) activations patterns, further disclosing auditory reactivity differences in specific brain networks between phasic and tonic REM sleep episodes (Wehrle et al. 2007).

2.2 Endogenous Brain Stimulation: The up and down of Slow Oscillations and Spindles

Simultaneous EEG/fMRI recordings have enabled researchers to revisit the PET-based concept of SWS as a stage of brain quiescence, reputedly characterized by global and regional decreases of brain activity. Indeed, animal research taught us that cortico-thalamocortical loops are involved in the generation of EEG spindles

(11–15 Hz) and delta waves (0.5–4 Hz), which in turn are organized by cortically generated slow oscillations (<1 Hz; Steriade 2001), and that these rhythms (under the control of brainstem and forebrain modulatory systems) are combined within specific time windows corresponding to the depolarizing phase (up state) of the slow oscillations (Steriade 2005). Dang-Vu et al. (2008) used an endogenous event-related approach to investigate using fMRI the transient changes in regional cerebral activity specifically associated with slow waves (<1 Hz; >140 μV) and delta waves (0.5–4 Hz; 75–140 μV) during NREM sleep. That is, the events of interest were defined based on the participant's own neurophysiological activity, e.g. the rising slope of each slow wave during SWS, rather than on the occurrence of an externally delivered, exogenous stimulus (like for instance a sound). Using this approach, they found increased activity coincident with the active depolarized ("up") state of oscillations (as indexed by peak negativity in the EEG) in several cortical areas including the inferior frontal and medial prefrontal cortices, and the precuneus and posterior cingulate areas, both for slow and delta waves. Besides these commonalities, slow oscillations (<1 Hz) were associated with increased activity in the parahippocampal gyrus, the cerebellum and the brainstem, whereas delta waves were specifically associated with increased activity in frontal areas (Fig. 2). Another study found infraslow (<0.1 Hz) oscillations in the EEG band positively correlated with brain activity mostly in subcortical regions including cerebellum, thalamus, basal ganglia and hippocampus, whereas these infraslow oscillations negatively correlated with cortical activity (Picchioni et al. 2011). Additionally in the Dang-Vu et al. (2008) study, increased activity associated with slow oscillations was found in the midbrain and the pontine tegmentum, a region that includes critical structures involved in the regulation of sleep and wakefulness, and this activation encompassed the noradrenergic locus coeruleus (LC). In line with animal data (Eschenko et al. 2012), these findings suggest that pontine structures are active in phase with slow oscillations, possibly to allow the brain periodically restoring microwake-like activity patterns facilitating neuronal interactions (Dang-Vu et al. 2008). Hence, EEG/fMRI studies confirm that human NREM sleep genuinely is an active state during which phasic increases in brain activity are synchronized to slow oscillations.

Another endogenous event-related fMRI study showed that the occurrence of phasic sleep spindles during NREM sleep is associated with increased brain activity in a cortico-subcortical network including the thalamus, paralimbic areas, and superior temporal gyri (Schabus et al. 2007). Besides, activity in different thalamocortical networks was associated with fast (13–15 Hz) and slow (11–13 Hz) spindles. Indeed, whereas slow spindles were associated with activation of the superior temporal gyrus, fast spindles preferentially recruited hippocampal and sensorimotor cortical areas, further supporting the hypothesis that fast and slow spindles rely upon two functionally separated systems (Fig. 2). Another study similarly found increased spindle-related activity in the thalami, putamen, posterior cingulate, paracentral and temporal cortices, and an additional association between the occurrence of K-complexes and increased activity in the thalami, superior temporal and medial occipital, parietal and frontal areas (Caporro et al. 2012).

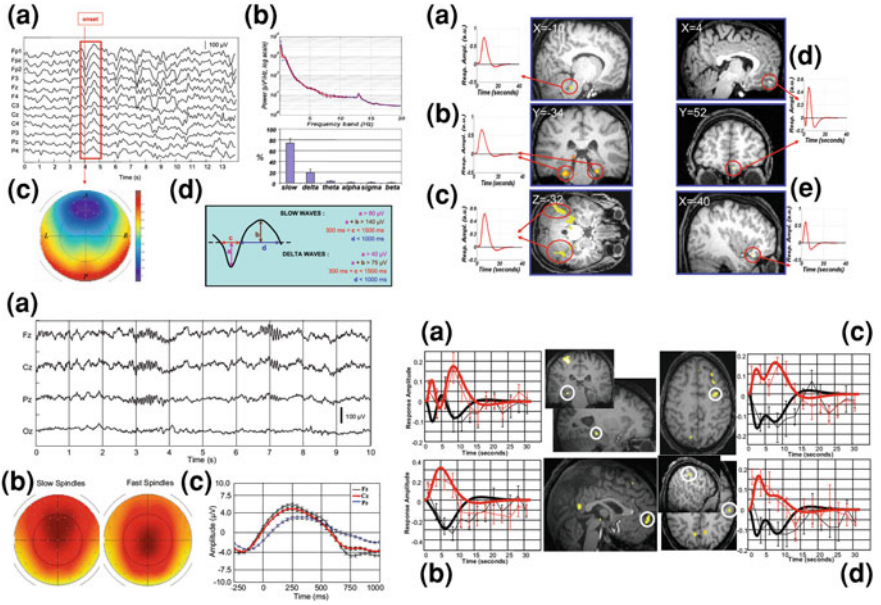

Fig. 2 Slow oscillations and spindles during NREM sleep investigated using endogenous event-related EEG-fMRI. *Left top* panel shows **a** detection of the onset of sleep EEG slow oscillations (peak negativity for sample wave framed in *red*); **b** EEG power spectrum; **c** topographical distribution of slow wave sleep epochs; and **d** criteria for separate detection of slow and delta waves. *Right top* panel shows brain regions specifically activated in relation to high amplitude slow waves (<1 Hz) (**a** Pontine tegmentum, **b** Parahippocampal gyrus, **c** Cerebellum) or in relation to delta waves (1–4 Hz) (**d** Medial prefrontal cortex, **e** Inferior frontal gyrus). Adapted with permission from Dang-Vu et al. 2008. *Left bottom* panel shows EEG characterization of sleep spindles with **a** representative spindles on a typical stage 2 sleep EEG recording after correction for fMRI-related artifacts; **b** topographical distribution of slow (11–13 Hz) and fast (13–15 Hz) spindles; and **c** EEG data (0.5–4 Hz) averaged with respect to the onset of all sleep spindles, showing that spindles start (time 0) on the depolarizing phase of the oscillation. *Right bottom* panel depicts differential fMRI activity (BOLD response) between fast and slow spindles. Larger brain responses for fast (*red*) than slow (*black*) spindles are revealed in the hippocampus (**a**), mesial prefrontal cortex (**b**), precentral gyrus (**c**), and postcentral gyrus (**d**). Side panels show the differential evolution of BOLD responses in fast and slow spindles. Adapted with permission from Schabus et al. 2007

2.3 *Endogenous Activity Modulates Brain Responsiveness to External Stimulation*

Both spindles and slow oscillations can modulate brain responsiveness to auditory stimulation during NREM sleep. Two studies showed persistent wake-like responses during NREM sleep except when spindles were present (Dang-Vu et al. 2011; Schabus et al. 2012) or stimulations occurred in the downward slope of the slow oscillation (Schabus et al. 2012), during which responses became less

consistent or even absent. Together with distinct N550 EEG responses to tones during sleep spindles (Schabus et al. 2012), this suggests that the brain is more responsive during the upward slope of the slow oscillation during deep NREM sleep. The authors propose that the presence of short temporal windows during which the brain is open to external stimuli during NREM sleep is consistent with the fact that even during deep sleep meaningful events can be detected.

2.4 Dynamic Interactions in REM Sleep

Although REM sleep has been less thoroughly investigated using this technique, fMRI resting-state connectivity analyses showed that activity in the so-called default-mode network (Raichle et al. 2001) is functionally uncoupled during NREM sleep (i.e. there is diminished connectivity) then recoupled during REM sleep where it is similar to wakefulness (Chow et al. 2013). Additionally however, REM sleep was specifically characterized by a widespread, temporally dynamic interaction between unimodal sensorimotor areas and higher-order association cortices (including in the default-mode network). Indeed, the two systems become anticorrelated and fluctuated rhythmically, reciprocally alternating epochs with a frequency ranging from 0.1 to 0.01 Hz. The functionality of these slowly alternating activation patterns remains unknown.

2.5 Phasic REM Events and the Source of Spindles

Finally, magnetoencephalography (MEG) is distinct from fMRI in that it is noise-free and operates on a neuronal timescale, i.e. within the scale of milliseconds while having good localizing power. Hence, its features offer interesting opportunities to track the time course and spatial evolution of the magnetic correlates of cerebral activity associated with both endogenous and exogenous events during sleep. For instance, MEG was used to investigate cortical responses to diverse sensory and/or noxious stimuli during sleep (Kakigi et al. 2003; Wang et al. 2004). Furthermore, MEG allowed the differentiation of cerebral networks activated before, during and after ocular saccades initiation during REMs in REM sleep (Corsi-Cabrera et al. 2008; Ioannides et al. 2004), or to compute the source location of maximal spindle activity, which was found in precentral and/or post-central areas (Gumenyuk et al. 2009). Finally, it is worth noting that combined EEG and MEG studies have revealed heterogeneous MEG sources for human sleep spindles suggesting that multiple generators are active, whereas sleep spindles as measured by the EEG seem to be generated by a different, diffusely synchronous system (Dehghani et al. 2010a, b). These results are in line with animal studies that identified two thalamo-cortical systems, i.e. the core and matrix systems, which produce focal or diffuse activation (Jones 1998). Further imaging

(Dehghani et al. 2011) and computational (Bonjean et al. 2012) investigations suggest that synchronous spindles captured by the EEG emerge from asynchronous spindles recorded using MEG, in line with the hypothesis that the spatial coherence for spindles in the EEG is actually a consequence of diffuse matrix projections of the thalamus to layer 1 compared with the focal projections of the core pathway to layer 4 recorded in the MEG (Destexhe and Sejnowski 2003). Hence, MEG represents a complementary and useful non-invasive tool to improve our understanding of the complex neurophysiological mechanisms that subtend sleep phenomena.

3 Neural Models of Memory Consolidation During Sleep

Memory consolidation refers to a temporal process lasting from a few minutes to several years by which initially fragile memory traces undergo a series of transformations eventually leading to their strengthening into long-term memory stores (McGaugh 1966). Memory consolidation and the progressive modification of the acquired information are instances of brain plasticity, i.e. the capacity of the brain to adapt its function and structure over time to accommodate novel experience. Thus reorganization of cortical networks, disinhibition of neuronal assemblies, modification and remodelling of synaptic connections can be seen as instances of memory formation and consolidation processes. In this respect, experimental evidence suggests that the neurophysiological conditions of sleep are favourable for the consolidation of novel memories and their durable inscription in long-term memory stores (Peigneux et al. 2011).

3.1 Neuronal Replay and the Hippocampal-Neocortical Dialogue

It has been proposed that memory consolidation relies on complementary learning systems subtended by different neuroanatomical structures (Marr 1971; McClelland 1994). In the first step, information is quickly learned but only temporarily held into a transitory memory store. Robust encryption then takes place at a slower rate in lasting memory stores. Repetitive interactions between transitory and lasting memory stores allow connections subtending new memory items to be gradually reorganized and reinforced. Hence, two-stage models assume a progressive transfer of the learned information from transitory to lasting memory stores, where it will be progressively integrated into pre-existing networks. Expanding on this framework, the hippocampal-cortical dialogue model (Buzsaki 1996) proposes that memory consolidation takes place through repeated interactions between transitory and lasting long-term memory stores across multiple iterations of the sleep-wake cycle.

During wakefulness, learning-related information collected at the neocortical level is transferred and transiently stored in the hippocampus. During NREM sleep, characterized by decreased cholinergic activity, information preferentially flows in the opposite direction, from hippocampal to neocortical stores (Hasselmo 1999).

Consequently, repeated activation of the acquired information in the hippocampus during post-learning NREM sleep will eventually lead to a progressive transfer toward neocortical long-term memory stores. Conversely, higher cholinergic levels during REM sleep would promote information feedback toward hippocampal repositories. Memories will thus be stored and consolidated for the long-term across repeated SWS-REM sleep cycles. It is surmised here that neuronal patterns in hippocampal and neocortical stores are synchronized by the alternation of "up" and "down" states of slow oscillations during SWS (Fig. 3), an interpretation in line with neuroimaging findings reporting differential brain responsiveness between these two states (e.g. see above Dang-Vu et al. 2008, 2011). More precisely, the high-frequency bursts of neuronal activity in the hippocampus (i.e. the sharp wave ripples) and the thalamo-cortical spindles are triggered during the depolarizing ("up") phase of the slow oscillations. These sharp waves ripples synchronize with spindles that then propagate within the neocortex, inducing long-term potentiation (LTP) processes that would eventually modify synaptic strengths in interconnected neuronal networks (Rosanova and Ulrich 2005), hence promoting a progressive transfer of hippocampus-dependent memories to neocortical stores. It remains debated whether the consolidated information is erased from hippocampal stores upon transfer, or whether hippocampal pointers still contribute retrieving the information stored in long-term memory as proposed by the multiple trace theory (Nadel et al. 2000). It is worth noting here that the hippocampal-neocortical model associates the consolidation process mostly with SWS and hippocampus-dependent declarative and spatial memories. A broader, less-specific variant called the "neuronal replay hypothesis" proposes that cortical or subcortical activation patterns associated with novel learning are reactivated during subsequent sleep stages (either NREM or REM stages), eventually leading to the replay of the learned information and its gradual integration and/or transfer into long-term memory stores, an assumption supported by neuroimaging data showing reactivation of learning-related activity both during REM (Maquet et al. 2000; Peigneux et al. 2003) and NREM sleep (Peigneux et al. 2004; Rasch et al. 2007).

3.2 Synaptic Homeostasis and Memory Consolidation

An alternative, but not exclusive model for memory consolidation during sleep is the synaptic homeostasis theory (SHY) (Tononi and Cirelli 2006). The theory proposes that memory consolidation benefits from the local use-dependent synaptic downscaling phenomenon that takes place during sleep, as a secondary consequence of the growth of synaptic connections associated with novel learning at wake. This model posits that memory acquisition during wakefulness is

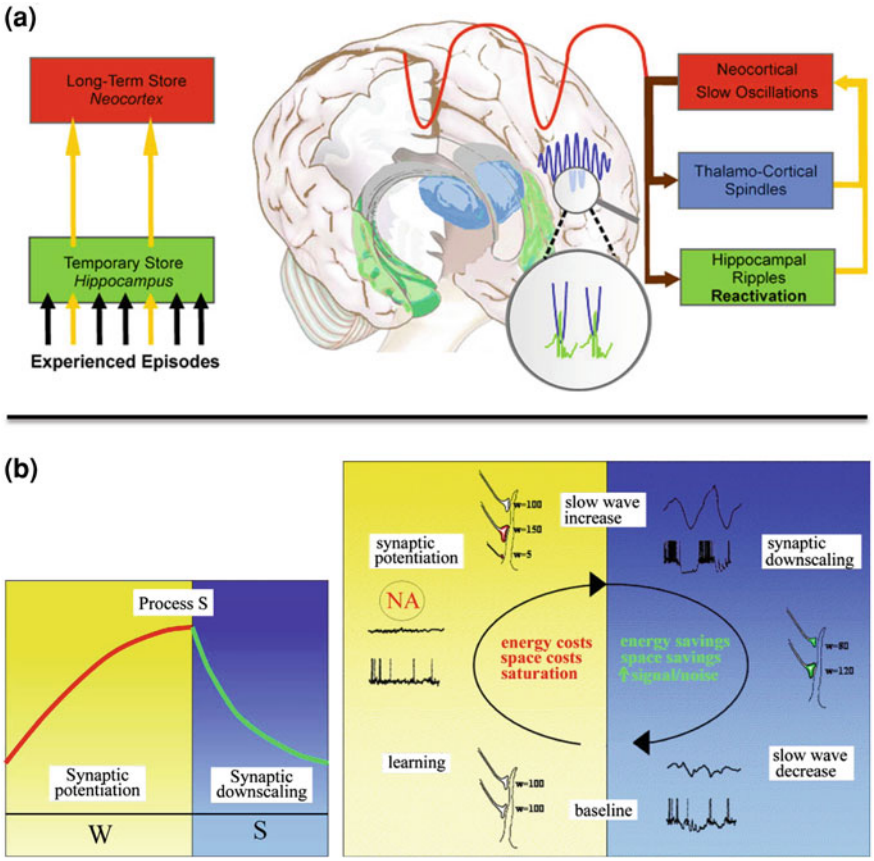

Fig. 3 Neural models of memory consolidation during sleep. **a** Hippocampal-neocortical dialogue. Information gained during novel experience is transiently stored in the hippocampus, and then progressively transferred into neocortical long-term memory stores. Transfer of information from hippocampal to neocortical areas during NREM sleep is promoted by SWS oscillations. Hippocampal ripples associated with the reactivation of the learned information are triggered during the depolarizing ("up") phase of the slow oscillations, and synchronized with thalamo-cortical spindles. Reprinted with permission from Born and Wilhelm 2011. **b** Synaptic homeostasis theory (SHY). Memory acquisition during wakefulness is associated with locally increased synaptic potentiation and elevated energy and space costs, eventually leading to the saturation of the learning-related neuronal network and decreased plasticity. Local neuronal saturation then leads to proportionally increased slow oscillatory activity during post-training NREM sleep, providing the necessary conditions to downscale synaptic strength to baseline level. This depotentiation process improves the signal-to-noise ratio in learning-related neuronal ensembles, consolidating the learned experience. Reprinted with permission from Tononi and Cirelli 2006

associated with locally increased synaptic potentiation and elevated energy and space costs, eventually leading to the saturation of the learning-related neuronal network and decreased plasticity. Local neuronal saturation will then lead to

proportionally increased slow oscillatory activity during post-training NREM sleep (Fig. 3). According to this model, homeostatically regulated slow oscillations during SWS offer optimal conditions to downscale synaptic strength to their baseline level, thus restoring the conditions for synaptic plasticity, while preserving the necessary differentiation between learning-related potentiated and other non-potentiated synapses. Hence slow oscillations would refine the synaptic weight and indirectly improve the signal-to-noise ratio in learning-related neuronal ensembles. In this context, weak memory traces will be removed and stronger traces remain, without the need for a transfer between remote brain structures. Consequently, this theory might be more appropriate to account for the consolidation of memories that are not dependent of the hippocampus, e.g. perceptual or motor memories processed at the neocortical level. In man, support for this theory was found in EEG studies showing locally increased slow oscillations during post-training NREM sleep in brain areas involved in a motor adaptation process (Huber et al. 2004; Landsness et al. 2009).

3.3 Dissociated and Integrated Memory Consolidation Processes Reconciled?

Despite different mechanisms and predictions, the hippocampo-neocortical and the synaptic homeostasis theories should not be seen as conflicting, as they more likely represent complementary phenomena in memory consolidation processes. For instance, increased hippocampal activity was observed using fMRI during the acquisition of an oculomotor sequence in fast-learning participants, who subsequently exhibited overnight improvement in performance, contrarily to slow-learning participants who did not initially engage hippocampal activity during learning and failed to improve performance overnight (Albouy et al. 2008). One can surmise that hippocampal tagging in fast learners actually reflects an initial homeostatic-like synaptic potentiation in hippocampal areas that might then trigger further processes possibly leading to the hippocampo-neocortical information transfer. Additionally, it must be mentioned that the role of REM sleep in the consolidation of recent memories is not considered much in these conceptualisations (although admittedly envisioned in the Buzsaki 1996 model), thus not entirely accounting for experimental evidence. For instance, combined EEG and fMRI data have yielded evidence for links between an overnight improvement of visual discrimination skills and the number of slow waves initiated in lateral occipital areas during post-training NREM sleep. This is paralleled by an association between the duration of REM sleep and increased oxygen consumption [i.e. higher Blood Oxygen Level Dependent (BOLD) response] at overnight retesting (Mascetti et al. 2013).

In this respect, the dual process (Plihal and Born 1997) and the sequential process (Giuditta 1984) hypotheses might more specifically acknowledge for the fact that both NREM and REM sleep stages are likely to contribute in the cascade of neuronal events eventually leading to memory consolidation. According to the

dual process hypothesis, NREM sleep would be especially suited for the consolidation of declarative, hippocampus-dependent memories, whereas REM sleep would subtend the consolidation of procedural (hippocampus-independent) memories (Plihal and Born 1997, 1999). However, this marked distinction between declarative and procedural memory processes as a function of sleep stages is far to be supported by the existing literature, that relates the consolidation of information belonging to a wide range of memory domains (from verbal to motor material) with NREM sleep-related processes (see Sect. 4). Alternatively, the sequential hypothesis proposes that effective memory consolidation actually requires different steps of information processing during NREM then REM sleep episodes (Ficca et al. 2000; Giuditta 1984), for instance protection of recent memories against interference during NREM then their consolidation during REM sleep (Scrima 1982).

4 Brain Plasticity and Memory Consolidation During Sleep

The contribution of sleep to memory consolidation is now widely acknowledged in the literature. Animal studies have supported the hypothesis that post-training sleep activity recorded in learning-related brain areas might represent the neural signature of memory-related cognitive processes. For instance, cell recording studies in the rat hippocampus and cortex following exposure to a spatial environment (Kudrimoti et al. 1999; Lee and Wilson 2002; Louie and Wilson 2001; Nadasdy et al. 1999; Pavlides and Winson 1989; Wilson and Mcnaughton 1994) and in the song area of young zebra finches (e.g. Dave et al. 1998; Dave and Margoliash 2000; Margoliash 2001) revealed neuronal replay phenomenon during sleep, suggesting the reactivation of neural activity associated with previous experience.

4.1 REM Sleep and the Neuronal Replay of Procedural Memories

In humans, evidence supporting the neural replay hypothesis was initially found using $H_2{}^{15}O$-PET. Brain areas activated during practice on a probabilistic serial reaction time (SRT) task, a form of implicit motor sequence learning (Cleeremans and McClelland 1991; Peigneux et al. 2000) were found more active during subsequent REM sleep in subjects previously trained on the task than in untrained subjects (Maquet et al. 2000; Fig. 4). In addition, rCBF in the left premotor cortex was correlated with activity in the pre-supplementary motor area and in the posterior parietal cortex involved in sequence learning, much more during post-training REM sleep than during REM sleep without a prior sequence learning experience (Laureys

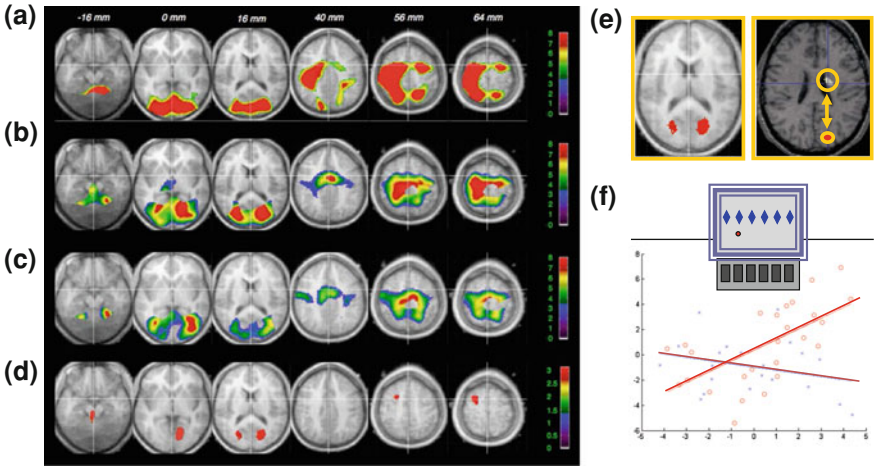

Fig. 4 Neuronal reactivation during REM sleep. **a** Brain areas where activity during active wakefulness is associated with learning on a motor procedural SRT task; **b** Brain areas active during REM sleep after learning on the SRT task; **c** Brain areas active during baseline REM sleep (no prior learning experience); **d** Brain areas where activity is significantly higher during REM sleep after SRT practice than during baseline REM sleep, and already active during learning; **e** Higher activity in cuneus during REM sleep after SRT practice than after practice of randomly presented stimuli; and **f** temporal correlations during post-training REM sleep between cuneus and striatum activity after practice on the probabilistic (*red*) but not on the random (*blue*) SRT. Adapted with permission from Maquet et al. 2000 and Peigneux et al. 2003

et al. 2001). This suggests that motor memory traces are replayed in the cortical network during REM sleep. Furthermore, reactivation in learning-related areas during REM sleep was specific to the reprocessing of the implicit rules driving the succession of the displayed locations in the sequence, more than to the mere optimization of basic visuomotor skills. Indeed, reactivation in learning-related areas during REM sleep was only found in subjects trained to the rules-based SRT task, but not in other participants trained on the same task but using a random material (Peigneux et al. 2003). These results indicate that the reactivation of local brain activity during REM sleep was related to the implicit acquisition of the probabilistic rules that defined stimulus sequences. Furthermore, learning-related cuneus activity during REM sleep also correlated with rCBF variations in the striatum, a key area in probabilistic sequence learning (Peigneux et al. 2000), significantly more in participants trained to the probabilistic than in those trained to the random SRT task (Fig. 4). Finally, the level of sequence learning achieved prior to sleep also correlated with increases in rCBF during REM sleep, suggesting that post-training cerebral reactivation is modulated by the strength of the memory traces developed during learning (Peigneux et al. 2003). None of these post-SRT learning effects was observed during NREM sleep. As a whole, these results support the hypothesis that REM sleep is involved in the reprocessing and optimization of the high-order, complex information contained in the material to be learned.

4.2 NREM Sleep and Reactivation of Hippocampus-Dependent Memories

Using this same probabilistic SRT task, no effects were observed during NREM sleep periods. This result is seemingly contradictory with animal findings that yielded evidence for neuronal reactivations during NREM sleep (but see e.g. Poe et al. 2000 and Louie and Wilson 2001 for experience-dependent changes in neuronal firing during REM sleep). One possibility for this apparent discrepancy is that learning complex sequential regularities in the probabilistic SRT task is dependent upon the activity of striato-cortical networks (Peigneux et al. 2000), whereas reactivations studies in rodents mostly used hippocampus-dependent spatial orientation tasks (e.g. Wilson and Mcnaughton 1994). In line with this interpretation, activity in hippocampal and medial temporal areas subtending navigation learning in a virtual town (i.e. a spatial, hippocampus-dependent learning task) was enhanced during subsequent NREM sleep, and mostly SWS (Peigneux et al. 2004), but not after training on the SRT task. In this PET study, hippocampal activity during post-training SWS was proportional to the overnight improvement in performance in the navigation task. These results suggest that learning-dependent modulation in hippocampal activity during human sleep actually reflects the offline processing of recent episodic and spatial memory traces, eventually leading to the plastic changes underlying subsequent improvements in performance. As a whole, PET studies indicate that distinct memory traces pertaining to different cerebral structures and memory systems, acquired under different learning conditions, are reactivated during subsequent and distinct sleep stages. Although these results seemingly concur with the dual process hypothesis positing that NREM sleep subtend consolidation of declarative, hippocampus-dependent memories whereas REM sleep subtend consolidation of procedural memories (e.g. Plihal and Born 1997, 1999), such conclusion should be taken thoughtfully. Indeed, the demonstration of segregated patterns of neuronal activity during different stages of sleep associated with the consolidation of different memory systems does not invalidate other interpretations. For instance, other neurophysiological mechanisms contributing to the memory consolidation processes might not have been detectable using the PET technique, limiting possible interpretations. Hence, these results do not allow rejecting alternative accounts, for instance, the sequential hypothesis (Giuditta 1984) assuming that effective memory consolidation requires information processing steps first during NREM then REM sleep episodes.

4.3 Neuronal Reactivations in the Light of Combined EEG/FMRI

Functional MRI also evidenced learning-related cerebral activation during sleep. After intensive training on a perceptual texture discrimination task, increased activity was observed during post-training SWS (versus the night before learning)

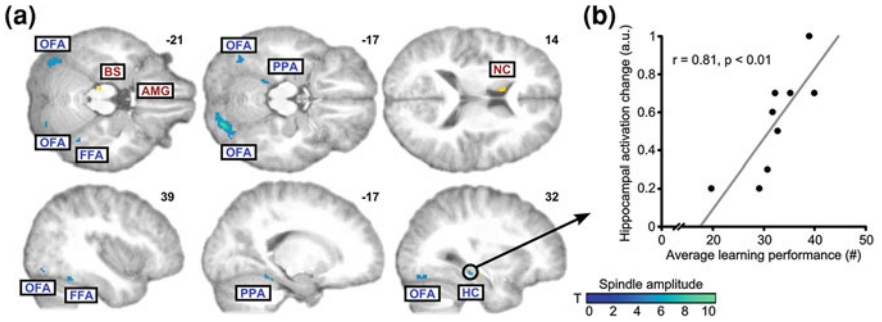

Fig. 5 Spindles, memory for face-scene associations and neuronal reactivation in the light of combined EEG-fMRI. **a** Brain areas showing learning-specific increases in coupling to spindle amplitude (cold colours) relative to control condition (*BS* brainstem; *FFA* fusiform face area; *HC* hippocampus; *NC* caudate nucleus; *OFA* occipital face area; *PPA* parahippocampal place area). **b** Correlation between learning performance and increased spindle-related hippocampal activity during subsequent sleep. Adapted with permission from Bergmann et al. 2012

in stimulated areas of the primary visual cortex (V1). Overnight improvements in behavioural performance additionally correlated with the amplitude of the BOLD signal in trained regions during SWS (Yotsumoto et al. 2009), in line with EEG findings of locally increased initiation of slow waves after training on visual orientation discrimination task (Mascetti et al. 2013). Similarly, sleep spindle-related reactivation after learning face-scene paired associates was observed in category-specific cortical areas during NREM sleep (Bergmann et al. 2012). In this EEG/fMRI study, learning face-scene associations triggered a stronger combined activation of neocortical and hippocampal regions during subsequent sleep, as compared to visuomotor practice. Also, reactivations were in temporal synchrony with spindle events and tuned by ongoing variations in spindle amplitude, but restricted to the face- and scene-selective visual cortical areas activated during pre-sleep learning. Finally, participant's performance at the end of learning was correlated with spindle-coupled hippocampal activation (Fig. 5). These results can be also interpreted in the framework of a prior EEG study showing that fast spindles are driven by the depolarizing *up* state of neocortical slow oscillations and enhance the likelihood of succeeding slow oscillations together with slow spindles. As prior learning enhanced this pattern, it suggests that slow oscillation-spindle cycles and fast spindles contribute in sleep-dependent memory and consolidation processes (Molle et al. 2011). Altogether, spontaneous reactivation studies suggest the reprocessing of previously learned information during post-learning sleep, a reactivation possibly organized by sleep spindles and slow oscillations in the case of hippocampal-neocortical memories.

4.4 Cueing Memories During Sleep

In a complementary approach, researchers have assumed that presenting learning-related cues during post-training sleep would trigger the reactivation of previously associated memory traces. Accordingly, non-awakening presentation during SWS of an odour associated with the learning of cards positions in the game "Memory" enhanced subsequent retrieval performance above levels achieved after a normal, undisturbed night of sleep (Rasch et al. 2007). Presentation of another odour was ineffective, demonstrating the specificity of the cueing effect. As well, presentation of the associated odour during REM sleep or wakefulness did not enhance performance. Functional MRI recordings additionally showed that cueing the associated odour during post-learning SWS triggered hippocampal BOLD responses, associated with performance improvement in the declarative memory task. Cueing-related consolidation of a finger-tapping motor procedural memory task was tested in the same study. At variance with the declarative paired association task however, re-presentation of the cue odour during SWS or REM sleep was ineffective to improve memory. This result is discrepant with other data suggesting that presentation of cues coincidently with REMs actually boost procedural learning. For instance, prior studies (Guerrien et al. 1989; Smith and Weeden 1990) found that cueing during post-training REM sleep using auditory stimulations delivered during learning improves behavioural performance when tested on the next day. Since odour pathways directly link to the hippocampus, it is possible that odour stimulation is not appropriate to trigger non hippocampus-dependent procedural memories, and that other sensory modalities should be exploited. Accordingly, another behavioural/EEG study trained participants to play two melodies on a keyboard. Auditory presentation of one of the two melodies during a post-learning subsequent nap resulted in higher performance improvement for the sleep-replayed than for the other melody (Antony et al. 2012), suggesting that auditory cueing during sleep is beneficial for sensorimotor memories to the same extent than odour cueing for non-declarative memories. However, auditory stimulations were delivered during NREM sleep again in this latter study, leaving under discussion the possibility to trigger memory consolidation processes during REM sleep. Notwithstanding, other studies confirmed that sounds are as effective as odours to trigger memory consolidation processes. In an EEG study (Rudoy et al. 2009), participants learned the location of different objects, each object being associated with a congruent sound (e.g. a bark associated with the image of a dog). During the subsequent nap, half of the object-associated sounds were delivered. Recall was higher for the cued than the non-cued images, again suggesting specificity in the triggered reactivations and in the ensuing consolidation processes. Similarly, participants were scanned during SWS using fMRI while presented the object-associated auditory cues (van Dongen et al. 2012). Although memory performance was similar in the experimental and control conditions, evoked BOLD responses in the right parahippocampal area were higher during SWS for the cued than for the control sounds. Furthermore, the connectivity

between the parahippocampal and the posterior visual areas increased upon presentation of the cue sounds. According to the authors, this suggests that cue-related evoked responses during sleep are not merely limited to the processing of auditory stimulations, but actually generalize to the visual areas recruited during the task. This effect is congruent with the report of spindle-related reactivation of paired associates both in hippocampal and task-specific face or locations-related areas (Bergmann et al. 2012).

5 Imaging the Effect of (a Lack of) Sleep on Memory Consolidation

Alternative and less constraining strategies have been devised to test the hypothesis that recently acquired memories are consolidated during sleep, without the need to record brain activity during sleep episodes. We have seen that reactivation studies globally rely on the assumption that post-training sleep processes promote plastic brain changes and consolidation of memories. Conversely, it can be assumed here that sleep deprivation should hamper sleep-related consolidation processes, eventually leading to an alteration of overnight memory performance and/or of the cerebral organization underlying access to consolidated memories.

5.1 Sleep Deprivation and the Consolidation of Procedural Memories

Pioneering the sleep deprivation strategy with neuroimaging methods, Maquet et al. (2003) trained participants on a motor pursuit task, a paradigm of procedural memory. Subjects were either sleep-deprived or allowed to sleep the night following training, then scanned using fMRI 3 days later while practicing again the pursuit task, both on new and previously learned trajectories. Sleep deprivation during the post-training night resulted in only a small improvement in performance for both trajectory types, whereas performance for the learned trajectories was selectively and dramatically enhanced in participants who slept after training. Additionally, the analysis of fMRI data showed that sleep deprivation hampered learning-related changes in cerebral connectivity in the superior temporal sulcus and cerebellum, and between frontal and supplementary eye fields, a connectivity that was found reinforced in the post-training sleep condition. Parallel changes in behavioural performance and cerebral activity patterns after periods of post-learning wakefulness versus sleep were also found using different fMRI settings both for the consolidation of motor and visual skill learning (Fischer et al. 2005; Walker et al. 2005a, b). In a more recent fMRI study (Albouy et al. 2012), performance in a visuomotor adaptation task was found to be stabilized after sleep but deteriorated after sleep

deprivation, hence disclosing a behavioural advantage of post-training sleep. Besides, participants deprived of sleep on the post-learning night continued to recruit cerebello-cortical networks involved at the earliest stages of visuomotor learning, whereas participants allowed to sleep after learning exhibited similar patterns of cerebral activity during learning and retest. Additionally, increased activity in hippocampal and frontal areas during learning was associated with a better resistance against the detrimental effects of sleep deprivation. As suggested by other fMRI studies, hippocampal activity during learning in interaction with activation within striatal structures might contribute to consolidating motor adaptation (Albouy et al. 2012) and motor sequential (Albouy et al. 2008, 2013a, b) skills. Hippocampal activity possibly contributes to consolidation by tagging at an early learning stage the memories to be consolidated during subsequent sleep episodes (Albouy et al. 2008), or by initiating at an earlier stage the process of consolidation, benefitting from continued post-training neural activity processes during wakefulness (Peigneux et al. 2006). However, the reorganization of brain patterns underlying performance for procedural memories after sleep is not necessarily accompanied by overt changes in behaviour. Indeed, sleep after implicit learning on a probabilistic SRT task is associated with a diminished differentiation between event-related fMRI responses for the items following versus those violating the sequential rules embedded in the material to be learned (Fig. 6), although overnight changes in performance were similar in the sleep and sleep-deprived post-learning conditions (Urbain et al. 2013). Modified BOLD responses were also found in a set of cortical and subcortical areas previously shown to be part of the network subtending implicit sequence learning (Peigneux et al. 2000) and its offline processing during REM sleep (Maquet et al. 2000; Peigneux et al. 2003). Also in the Urbain et al. (2013) study, likewise prior studies using the probabilistic SRT task (Maquet et al. 2000; Peigneux et al. 2003), there was actually no hippocampal activity associated with the acquisition process. This may suggests that the hippocampal tagging associated with motor sequence learning in other studies, thought to predict sleep-dependent improvement (Albouy et al. 2008, 2013a, b), relates to the deterministic and spatially predictable succession of the elements in learned sequences. Whereas, such spatially-based mapping is not possible for a less predictable succession of stimuli in the probabilistic SRT task, hence preventing hippocampal tagging.

5.2 Sleep Deprivation Changes the Neural Substrate of Declarative Memories

Studies conducted in the declarative memory domain also yielded evidence for an effect of post-training sleep deprivation on the consolidation of verbal and non-verbal, hippocampus-dependent material. As discussed above, van Dongen et al. (2012) demonstrated higher evoked BOLD responses for cued than control sounds

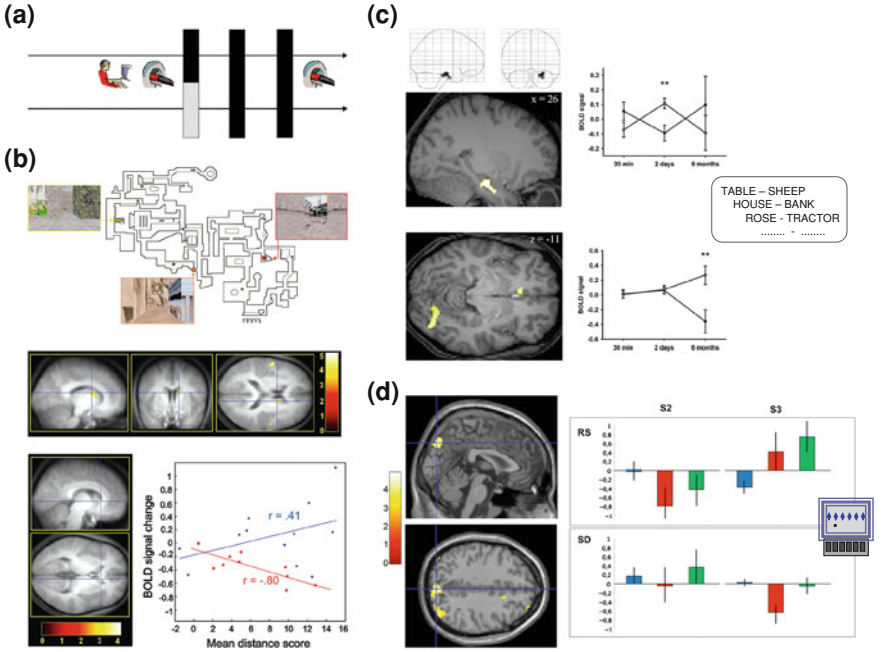

Fig. 6 Imaging the effects of sleep loss on the neural substrates of memories. **a** Typical sleep deprivation paradigm. Participants are trained on a novel task then tested for retrieval in the fMRI scanner, and then are either kept awake for the night (sleep deprivation, *grey bar*) or allowed to sleep normally (regular sleep, *black bar*). After two supplementary nights (*black bars*) aimed at ensuring that subsequent brain recordings will not be impeded by sleep deprivation-related effects, participants are retested at Day 4 during memory retrieval in the fMRI scanner. **b** Sleep-dependent shifts in the brain substrate of topographical learning. In participants allowed sleeping after topographical learning (i.e. finding routes in a virtual town), navigation performance becomes associated with activity in striatal regions (*red dots*), which is not the case in participants deprived of sleep on the first post-training night, in whom performance remains associated with hippocampal activity (Orban et al. 2006; Rauchs et al. 2008a, b). **c** Hippocampal-neocortical transfer or memories on the long-term. Successful retrieval of learned word pairs is associated with higher hippocampal activity in participants allowed to sleep on the post-training night (as compared to sleep deprived participants) when tested 2 days after learning, but no longer 6 months later. Conversely, activity in the medial prefrontal cortex is modulated by post-training sleep during successful word pairs retrieval 6 months after learning, but not after 2 days, giving support to the hypothesis that sleep promotes a progressive transfer of information from hippocampal to neocortical long-term memory stores (Gais et al. 2007). **d** Sleep-dependent neurophysiological processes in implicit sequence learning. In participants trained on a probabilistic SRT task then allowed to sleep after learning, there is diminished differentiation between event-related BOLD responses for items following versus those violating the sequential rules embedded in the material to be learned, although overnight changes in performance are similar in the sleep and sleep-deprived post-learning conditions (Urbain et al. 2013). Adapted with permission from Orban et al. 2006; Gais et al. 2007 and Urbain et al. 2013

in parahippocampal regions during SWS after learning object-location associations. Additionally, retrieval of reactivated object-location associations, but not retrieval of non-cued associations, correlated with pre- to post-sleep connectivity changes between parahippocampal and medial prefrontal areas. These results indicate that cueing during sleep may also modify connectivity patterns within the cerebral networks subtending memory retrieval at wake. Nonetheless, performance similarly improved for cued and uncued associations after sleep, hence failing to demonstrate a specific effect of sleep at the behavioural level. Therefore, it also shows that like in the procedural memory domain, reorganization of brain activity patterns underlying performance after sleep is not necessarily accompanied by overt changes in behaviour. Orban et al. (2006); Rauchs et al. (2008b) first evidenced this dissociation between recorded cerebral activity and behaviour, by showing that post-learning sleep promotes a shift in cerebral activity patterns underlying topographical memories. Participants were scanned during route-finding tasks immediately after learning their way in a virtual town and 3 days later. Half of them were allowed regular sleep, whereas the other half was totally sleep-deprived during the first post-learning night. Results disclosed a striking dissociation between unchanged behavioural performance and distinctive neural bases for route retrieval at delayed testing in sleep versus sleep-deprived participants. Whereas route finding elicited increased activity in a well-known navigation-related hippocampo-neocortical network (e.g. Maguire et al. 1998) at immediate and delayed retrieval both in sleep and sleep-deprived participants, activity in routine behaviour-related striatal areas was associated with delayed retrieval activity only in participants allowed to sleep after training (Fig. 6). Furthermore, higher activity in the striatum was associated with higher navigation accuracy in the sleep condition, whereas the relationship was reversed in sleep-deprived participants. These data suggest that brain activity is reorganized during post-training sleep in such a way that navigation, initially based on a hippocampus-dependent spatial strategy, becomes progressively contingent on a response-based strategy mediated by the striatum. A follow-up study investigated whether sleep globally promotes consolidation of all memory components embedded in virtual navigation (Rauchs et al. 2008a), or rather favours the development of specific representations (Rauchs et al. 2008b). Again, behavioural performance did not differ between participants allowed regular sleep during the post-learning night and those who were sleep deprived, neither when tested in a natural setting that engages both spatial and contextual memory processes nor when looking more specifically at each of these memory components. At the neuronal level however, fMRI analyses disclosed sleep-dependent changes in the cerebral activity subtending memory retrieval in each of these experimental conditions. This further shows that covert changes in cerebral responses might precede, or exist without, overt changes in behaviour.

5.3 *Long-Term Consequences of Sleep Deprivation on the Consolidation of Memories*

The sleep-dependent phenomenon is not unique to spatial learning. Indeed, a lack of overt changes in behaviour paralleled with covert modulations of brain activity following sleep has been reported also using verbal and emotional material. Additionally, sleep-dependent changes in brain activity have been evidenced on the long-term. Hippocampal activity during the retrieval of previously learned pairs of words was found to be higher 2 days later in participants who had slept as compared to those who were kept awake the night after learning, but not when tested 6 months later. The reverse pattern was found in the medial prefrontal cortex, where activity was similar 2 days after learning but word retrieval-related activity was enhanced 6 months later in the post-training sleep condition (Gais et al. 2007; Fig. 6). Similarly, a consistent decrease in hippocampal activity was observed during recognition of learned pictures over a 3-month period, whereas activity gradually increased in the ventral medial prefrontal cortex (Takashima et al. 2006). Additionally, functional MRI studies disclosed larger emotional stimulus retrieval-related responses 3 days after learning in the hippocampus and medial prefrontal cortex in the sleep condition as compared to the sleep deprived condition. This short-term increase in the BOLD response to emotional material was associated with a higher sleep-dependent connectivity and the additional involvement of emotion-related responses in the amygdala (Sterpenich et al. 2007), followed 6 months later by increased connectivity patterns between long-term neocortical stores and emotion-related areas (Sterpenich et al. 2009). These studies support the hippocampal-neocortical dialogue hypothesis (Buzsaki 1996) of a progressive transfer of the information from hippocampal toward neocortical stores over time and sleep, and suggest that this process might be modulated by additional parameters such as emotion or contextual information.

6 Conclusions

Non-invasive neuroimaging studies conducted in the past two decades have markedly increased our knowledge of the functional neuroanatomy of sleep and sleep stages, and have helped us to understand how sleep-related processes contribute to the consolidation of memories. Following PET studies that revealed regional patterns of cerebral activity characterizing the specificity of vigilance states in man, fMRI and MEG investigations have allowed a better understanding of the source and organization of synchronous oscillations in SWS. Additionally, these studies shed light on the organization and regulation of phasic events such as sleep spindles. The role of NREM sleep has been thoroughly studied, but REM sleep still deserves in-depth scrutiny to gain a similar level of understanding about its underlying neural mechanisms and function.

Neuroimaging studies also provided support for contemporary neural models for memory consolidation, indicating that these models are not opposite but might be seen as complementary mechanisms in the cascade of events leading to the enduring storage of recent memories. Whereas the so-called reactivation studies have shown that the neural activity during the acquisition of novel information can be recapitulated during post-training sleep, cueing paradigms additionally indicated that selected external stimuli modulate and might even enhance the process of consolidation during sleep. Finally, studies conducted using sleep deprivation paradigms have shown, as a counterpoint to reactivation studies, that post-training sleep deprivation impedes the reorganization and optimization of memory-related cerebral activity patterns at delayed retrieval. Also, they demonstrated that sleep-dependent changes in memory-related brain activity patterns could be dissociated from changes (or not) in behavioural performance, suggesting that long-term memory consolidation can be achieved using different cerebral strategies.

Further progress might be expected from a combination of existing neuroimaging and neurophysiological techniques. We now have the technical capabilities to perform multimodal recordings and even simultaneous stimulation (e.g. using transcranial direct current stimulation) of brain activity during natural sleep. The combination of these methods should allow us to gain a deeper understanding of the neurophysiological basis of the symphony of brain oscillations during sleep, and the role of these oscillations in memory consolidation. At the current stage however, we also need to use our technical capabilities and existing knowledge to investigate the sleep-related pathophysiological mechanisms leading to disruptions in brain plasticity and memory consolidation. For instance, evidence suggests that nocturnal interictal epileptic activity in idiopathic epilepsies disrupts SWS-related synaptic homeostatic processes underlying brain plasticity mechanisms (Bolsterli et al. 2011; Bolsterli Heinzle et al. 2014) and leads to overnight memory consolidation deficits, that can however disappear after the initiation of a pharmaceutical treatment normalizing (i.e. suppressing) nocturnal epileptic activity (Urbain et al. 2011). Imaging brain activity under pathological and normalized interictal conditions might help us understanding the impact of paroxysmal activities on the organization of the cerebral networks subtending memory consolidation. Along these lines, neuroimaging approaches might also help us unraveling the neurophysiological mechanisms underlying the relationships between sleep disorders and mental health problem. Hopefully, this will ultimately help to increase the range of possible therapeutic interventions.

Further progress may also arise from increased collaboration and back-and-forth communication between animal and human research. Animal research is crucial to provide novel research directions to develop hypothesis-driven studies in man. For instance, animal research recently demonstrated that sleep in mice is associated with a dramatic increase in the volume of the interstitial space, resulting in increased convective exchanges of cerebrospinal fluid with interstitial fluid, and in turn increasing the rate of beta-amyloid clearance during sleep. This process is disrupted by sleep deprivation (Xie et al. 2013). Beta-amyloid accumulation is a well-known hallmark of Alzheimer's disease (AD), a neurodegenerative pathology

characterized not only by long-term memory deficits but also by disturbances in circadian rhythms and sleep. Whether sleep disruptions are an aggravating factor in the formation of amyloid plaques in AD, eventually leading to impaired brain connectivity, should be investigated further, using a combination of neuroimaging and polysomnographic recordings. Hence animal research can provide novel directions to understand the disrupted neurophysiological mechanisms subtending learning and memory processes in relation with sleep.

References

Albouy G, King B, Maquet P, Doyon J (2013a) Hippocampus and striatum: dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. Hippocampus. doi:10.1002/hipo.22183

Albouy G, Sterpenich V, Balteau E, Vandewalle G, Desseilles M, Dang-Vu T, Darsaud A, Ruby P, Luppi PH, Degueldre C, Peigneux P, Luxen A, Maquet P (2008) Both the hippocampus and striatum are involved in consolidation of motor sequence memory. Neuron 58:261–272

Albouy G, Sterpenich V, Vandewalle G, Darsaud A, Gais S, Rauchs G, Desseilles M, Boly M, Dang-Vu T, Balteau E, Degueldre C, Phillips C, Luxen A, Maquet P (2013b) Interaction between hippocampal and striatal systems predicts subsequent consolidation of motor sequence memory. PLoS ONE 8:e59490. doi:10.1371/journal.pone.0059490

Albouy G, Vandewalle G, Sterpenich V, Rauchs G, Desseilles M, Balteau E, Degueldre C, Phillips C, Luxen A, Maquet P (2012) Sleep stabilizes visuomotor adaptation memory: a functional magnetic resonance imaging study. J Sleep Res. doi:10.1111/j.1365-2869.2012.01059.x

Andersson JLR, Onoe H, Hetta J, Lidstrom K, Valind S, Lilja A, Sundin A, Fasth KJ, Westerberg G, Broman JE, Watanabe Y, Langstrom B (1998) Brain networks affected by synchronized sleep visualized by positron emission tomography. J Cereb Blood Flow Metab 18:701–715

Antony J, Gobel E, O'Hare J, Reber P, Paller K (2012) Cued memory reactivation during sleep influences skill learning. Nat Neurosci 15:1114–1116. doi:10.1038/nn.3152

Bassetti C, Vella S, Donati F, Wielepp P, Weder B (2000) SPECT during sleepwalking. Lancet 356:484–485

Bergmann T, Molle M, Diedrichs J, Born J, Siebner H (2012) Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. Neuroimage 59:2733–2742. doi:10.1016/j.neuroimage.2011.10.036

Bolsterli B, Schmitt B, Bast T, Critelli H, Heinzle J, Jenni O, Huber R (2011) Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). Clin Neurophysiol 122:1779–1787. doi:10.1016/j.clinph.2011.01.053

Bolsterli Heinzle BK, Fattinger S, Kurth S, Lebourgeois MK, Ringli M, Bast T, Critelli H, Schmitt B, Huber R (2014) Spike wave location and density disturb sleep slow waves in patients with CSWS (continuous spike waves during sleep). Epilepsia. doi:10.1111/epi.12576

Bonjean M, Baker T, Bazhenov M, Cash S, Halgren E, Sejnowski T (2012) Interactions between core and matrix thalamocortical projections in human sleep spindle synchronization. J Neurosci 32:5250–5263. doi:10.1523/JNEUROSCI.6141-11.2012

Born J, Wilhelm I (2011) System consolidation of memory during sleep. Psychol Res 76(2):192–203

Braun AR, Balkin TJ, Wesensten NJ, Carson RE, Varga M, Baldwin P, Selbie S, Belenky G, Herscovitch P (1997) Regional cerebral blood flow throughout the sleep-wake cycle—an (H2O)-O-15 PET study. Brain 120:1173–1197

Buchsbaum MS, Gillin JC, Wu J, Hazlett E, Sicotte N, Dupont RM, Bunney WE (1989) Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. Life Sci 45:1349–1356

Buchsbaum MS, Hazlett EA, Wu J, Bunney J, William E (2001) Positron emission tomography with deoxyglucose-F18 imaging of sleep. Neuropsychopharmacology 25:S50–S56

Buzsaki G (1996) The hippocampo-neocortical dialogue. Cereb Cortex 6:81–92

Caporro M, Haneef Z, Yeh H, Lenartowicz A, Buttinelli C, Parvizi J, Stern J (2012) Functional MRI of sleep spindles and K-complexes. Clin Neurophysiol 123:303–309. doi:10.1016/j.clinph.2011.06.018

Chow H, Horovitz S, Carr W, Picchioni D, Coddington N, Fukunaga M, Xu Y, Balkin T, Duyn J, Braun A (2013) Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of consciousness. Proc Nat Acad Sci U.S.A 110:10300–10305. doi:10.1073/pnas.1217691110

Cleeremans A, McClelland JL (1991) Learning the structure of event sequences. J Exp Psychol Gen 120:235–253

Corsi-Cabrera M, Guevara M, del Rio-Portilla Y (2008) Brain activity and temporal coupling related to eye movements during REM sleep: EEG and MEG results. Brain Res 1235:82–91. doi:10.1016/j.brainres.2008.06.052

Czisch M, Wehrle R, Kaufmann C, Wetter TC, Holsboer F, Pollmacher T, Auer DP (2004) Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. Eur J Neurosci 20:566–574

Czisch M, Wetter TC, Kaufmann C, Pollmacher T, Holsboer F, Auer DP (2002) Altered processing of acoustic stimuli during sleep: reduced auditory activation and visual deactivation detected by a combined fMRI/EEG study. Neuroimage 16:251–258

Dang-Vu T, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M, Degueldre C, Balteau E, Phillips C, Luxen A, Sejnowski T, Maquet P (2011) Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. Proc Nat Acad Sci U.S.A 108:15438–15443. doi:10.1073/pnas.1112503108

Dang-Vu TT, Desseilles M, Laureys S, Degueldre C, Perrin F, Phillips C, Maquet P, Peigneux P (2005) Cerebral correlates of delta waves during non-REM sleep revisited. Neuroimage 28:14–21

Dang-Vu TT, Schabus M, Desseilles M, Albouy G, Boly M, Darsaud A, Gais S, Rauchs G, Sterpenich V, Vandewalle G, Carrier J, Moonen G, Balteau E, Degueldre C, Luxen A, Phillips C, Maquet P (2008) Spontaneous neural activity during human slow wave sleep. Proc Nat Acad Sci U.S.A 105:15160–15165

Datta S (1999) PGO wave generation: mechanism and functional significance. In: Mallick BN, Inoue S (eds) Rapid eye movement sleep. Narosa, New Delhi, pp 91–106

Dauvilliers Y, Boudousq V, Lopez R, Gabelle A, De Cock VC, Bayard S, Peigneux P (2011) Increased perfusion in supplementary motor area during a REM sleep behaviour episode. Sleep Med 12:531–532. doi:10.1016/j.sleep.2011.02.003

Dave A, Yu A, Margoliash D (1998) Behavioral state modulation of auditory activity in a vocal motor system. Science 282:2250–2254

Dave AS, Margoliash D (2000) Song replay during sleep and computational rules for sensorimotor vocal learning. Science 290:812–816

Dehghani N, Cash S, Chen C, Hagler DJ, Huang M, Dale A, Halgren E (2010a) Divergent cortical generators of MEG and EEG during human sleep spindles suggested by distributed source modeling. PLoS ONE 5:e11454. doi:10.1371/journal.pone.0011454

Dehghani N, Cash S, Halgren E (2011) Emergence of synchronous EEG spindles from asynchronous MEG spindles. Hum Brain Mapp. doi:10.1002/hbm.21183

Dehghani N, Cash S, Rossetti A, Chen C, Halgren E (2010b) Magnetoencephalography demonstrates multiple asynchronous generators during human sleep spindles. J Neurophysiol 104:179–188. doi:10.1152/jn.00198.2010

Desseilles M, Vu T, Maquet P (2011) Functional neuroimaging in sleep, sleep deprivation, and sleep disorders. Handb Clin Neurol 98:71–94. doi:10.1016/B978-0-444-52006-7.00006-X

Destexhe A, Sejnowski T (2003) Interactions between membrane conductances underlying thalamocortical slow-wave oscillations. Physiol Rev 83:1401–1453. doi:10.1152/physrev.00012.2003

Eschenko O, Magri C, Panzeri S, Sara S (2012) Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. Cereb Cortex 22:426–435. doi:10.1093/cercor/bhr121

Ficca G, Lombardo P, Rossi L, Salzarulo P (2000) Morning recall of verbal material depends on prior sleep organization. Behav Brain Res 112:159–163

Fischer S, Nitschke M, Melchert U, Erdmann C, Born J (2005) Motor memory consolidation in sleep shapes more effective neuronal representations. J Neurosci 25:11248–11255. doi:10.1523/JNEUROSCI.1743-05.2005

Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M, Rauchs G, Schabus M, Sterpenich V, Vandewalle G, Maquet P, Peigneux P (2007) Sleep transforms the cerebral trace of declarative memories. Proc Nat Acad Sci U.S.A 104:18778–18783

Giuditta A (1984) A sequential hypothesis for the function of sleep. In: Koella WP, Rüther E, Schulz H (eds) Sleep 84'. Hustav Fischer, New York, pp 222–224

Guerrien A, Dujardin K, Mandai O, Sockeel P, Leconte P (1989) Enhancement of memory by auditory stimulation during postlearning REM sleep in humans. Physiol Behav 45:947–950

Gumenyuk V, Roth T, Moran J, Jefferson C, Bowyer S, Tepley N, Drake C (2009) Cortical locations of maximal spindle activity: magnetoencephalography (MEG) study. J Sleep Res 18:245–253. doi:10.1111/j.1365-2869.2008.00717.x

Hasselmo ME (1999) Neuromodulation: acetylcholine and memory consolidation. Trends in Cognitive Sciences 3:351–359

Hofle N, Paus T, Reutens D, Fiset P, Gotman J, Evans AC, Jones BE (1997) Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. J Neurosci 17:4800–4808

Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78–81

Ioannides AA, Corsi-Cabrera M, Fenwick PB, del Rio Portilla Y, Laskaris NA, Khurshudyan A, Theofilou D, Shibata T, Uchida S, Nakabayashi T, Kostopoulos GK (2004) MEG tomography of human cortex and brainstem activity in waking and REM sleep saccades. Cereb Cortex 14:56–72

Jones EG (1998) Viewpoint. The core and matrix of thalamic organization. Neuroscience 85:331–345

Kajimura N, Uchiyama M, Takayama Y, Uchida S, Uema T, Kato M, Sekimoto M, Watanabe T, Nakajima T, Horikoshi S, Ogawa K, Nishikawa M, Hiroki M, Kudo Y, Matsuda H, Okawa M, Takahashi K (1999) Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. J Neurosci 19:10065–10073

Kakigi R, Naka D, Okusa T, Wang X, Inui K, Qiu Y, Tran TD, Miki K, Tamura Y, Nguyen TB (2003) Sensory perception during sleep in humans: a magnetoencephalograhic study. Sleep Med 4(6):493–507

Kaufmann C, Wehrle R, Wetter TC, Holsboer F, Auer DP, Pollmacher T, Czisch M (2006) Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study. Brain 129:655–667. doi:10.1093/brain/awh686

Kudrimoti HS, Barnes CA, Mcnaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19:4090–4101

Landsness E, Crupi D, Hulse B, Peterson M, Huber R, Ansari H, Coen M, Cirelli C, Benca R, Ghilardi M, Tononi G (2009) Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. Sleep 32:1273–1284

Laureys S, Peigneux P, Phillips C, Fuchs S, Degueldre C, Aerts J, Del Fiore G, Petiau C, Luxen A, van der Linden M, Cleeremans A, Smith C, Maquet P (2001) Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep. Neuroscience 105:521–525

Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36:1183–1194
Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29:145–156
Lydic R, Baghdoyan HA, Hibbard L, Bonyak EV, DeJoseph MR, Hawkins RA (1991) Regional brain glucose metabolism is altered during rapid-eye movement sleep in the cat: a preliminary study. J Comp Neurol 304:517–529
Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, OKeefe J (1998) Knowing where and getting there: a human navigation network. Science 280:921–924
Maquet P (2000) Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 9:207–231
Maquet P (2005) Current status of brain imaging in sleep medicine. Sleep Med Rev 9:155–156
Maquet P, Degueldre C, Delfiore G, Aerts J, Péters J-M, Luxen A, Franck G (1997) Functional neuroanatomy of human slow wave sleep. J Neurosci 17:2807–2812
Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R, Franck G (1992) Cerebral glucose utilization during stage 2 sleep in man. Brain Res 571:149–153
Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R, von Frenckell R, Franck G (1990) Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method. Brain Res 513:136–143
Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, del Fiore G, Degueldre C, Meulemans T, Luxen A, Franck G, van der Linden M, Smith C, Cleeremans A (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3:831–836
Maquet P, Péters J-M, Aerts J, Delfiore G, Degueldre C, Luxen A, Franck G (1996) Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383:163–166
Maquet P, Phillips C (1998) Functional brain imaging of human sleep. J Sleep Res 7:42–47
Maquet P, Schwartz S, Passingham R, Frith C (2003) Sleep-related consolidation of a visuomotor skill: brain mechanisms as assessed by functional magnetic resonance imaging. J Neurosci 23:1432–1440
Margoliash D (2001) Do sleeping birds sing? Population coding and learning in the bird song system. Prog Brain Res 130:319–331
Marr D (1971) Simple memory: a theory for archicortex. Philos Trans R Soc B: Biol Sci 262:23–81
Mascetti L, Muto V, Matarazzo L, Foret A, Ziegler E, Albouy G, Sterpenich V, Schmidt C, Degueldre C, Leclercq Y, Phillips C, Luxen A, Vandewalle G, Vogels R, Maquet P, Balteau E (2013) The impact of visual perceptual learning on sleep and local slow-wave initiation. J Neurosci 33:3323–3331. doi:10.1523/JNEUROSCI.0763-12.2013
McClelland JL (1994) The organization of memory. A parallel distributed processing perspective. Rev Neurologique 150:570–579
McGaugh JL (1966) Time-dependent processes in memory storage. Science 153:1351–1358
Molle M, Bergmann T, Marshall L, Born J (2011) Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep 34:1411–1421. doi:10.5665/SLEEP.1290
Nadasdy Z, Hirase H, Czurko A, Csicsvari J, Buzsaki G (1999) Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 19:9497–9507
Nadel L, Samsonovich A, Ryan L, Moscovitch M (2000) Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus 10:352–368. doi:10.1002/1098-1063(2000)10:4<352:AID-HIPO2>3.0.CO;2-D
Nofzinger EA (2004) What can neuroimaging findings tell us about sleep disorders? Sleep Med 5(Suppl 1):S16–S22
Nofzinger EA, Mintun MA, Price J, Meltzer CC, Townsend D, Buysse DJ, Reynolds CF III, Dachille M, Matzzie J, Kupfer DJ, Moore RY (1998) A method for the assessment of the functional neuroanatomy of human sleep using FDG PET. Brain Res Brain Res Protoc 2:191–198

Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, Moore RY (1997) Forebrain activation in REM sleep: an FDG PET study. Brain Res 770:192–201

Orban P, Rauchs G, Balteau E, Degueldre C, Luxen A, Maquet P, Peigneux P (2006) Sleep after spatial learning promotes covert reorganization of brain activity. Proc Nat Acad Sci U.S.A 103:7124–7129

Pavlides C, Winson J (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. J Neurosci 9:2907–2918

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44:535–545

Peigneux P, Laureys S, Fuchs S, Delbeuck X, Degueldre C, Aerts J, Delfiore G, Luxen A, Maquet P (2001) Generation of rapid eye movements during paradoxical sleep in humans. Neuroimage 14:701–708

Peigneux P, Laureys S, Fuchs S, Destrebecqz A, Collette F, Delbeuck X, Phillips C, Aerts J, del Fiore G, Degueldre C, Luxen A, Cleeremans A, Maquet P (2003) Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. Neuroimage 20:125–134

Peigneux P, Maquet P, Meulemans T, Destrebecqz A, Laureys S, Degueldre C, Delfiore G, Aerts J, Luxen A, Franck G, Van der Linden M, Cleeremans A (2000) Striatum forever, despite sequence learning variability: a random effect analysis of PET data. Hum Brain Mapp 10:179–194

Peigneux P, Orban P, Balteau E, Degueldre C, Luxen A, Laureys S, Maquet P (2006) Offline persistence of memory-related cerebral activity during active wakefulness. PLoS Biol 4:e100

Peigneux P, Urbain C, Schmitz R (2011) Sleep and the Brain. In: Espie C, Morin C (eds) Oxford Handbook of Sleep and Sleep Disorders. Oxford University Press, New York, pp 11–37

Picchioni D, Horovitz S, Fukunaga M, Carr W, Meltzer J, Balkin T, Duyn J, Braun A (2011) Infraslow EEG oscillations organize large-scale cortical-subcortical interactions during sleep: a combined EEG/fMRI study. Brain Res 1374:63–72. doi:10.1016/j.brainres.2010.12.035

Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9:534–547

Plihal W, Born J (1999) Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 36:571–582

Poe GR, Nitz DA, Mcnaughton BL, Barnes CA (2000) Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. Brain Res 855:176–180

Portas CM, Krakow K, Allen P, Josephs O, Armony JL, Frith CD (2000) Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. Neuron 28:991–999

Raichle M, MacLeod A, Snyder A, Powers W, Gusnard D, Shulman G (2001) A default mode of brain function. Proc Nat Acad Sci U.S.A 98:676–682. doi:10.1073/pnas.98.2.676

Rasch B, Buchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315:1426–1429. doi:10.1126/science.1138581

Rauchs G, Orban P, Balteau E, Schmidt C, Degueldre C, Luxen A, Maquet P, Peigneux P (2008a) Partially segregated neural networks for spatial and contextual memory in virtual navigation. Hippocampus 18:503–518. doi:10.1002/hipo.20411

Rauchs G, Orban P, Schmidt C, Albouy G, Balteau E, Degueldre C, Schnackers C, Sterpenich V, Tinguely G, Luxen A, Maquet P, Peigneux P (2008b) Sleep modulates the neural substrates of both spatial and contextual memory consolidation. PLoS ONE 3:e2949

Rosanova M, Ulrich D (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25:9398–9405

Rudoy J, Voss J, Westerberg C, Paller K (2009) Strengthening individual memories by reactivating them during sleep. Science 326:1079. doi:10.1126/science.1179013

Schabus M, Dang-Vu T, Albouy G, Balteau E, Boly M, Carrier J, Darsaud A, Degueldre C, Desseilles M, Gais S, Phillips C, Rauchs G, Schnakers C, Sterpenich V, Vandewalle G, Luxen A, Maquet P (2007) Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Nat Acad Sci U.S.A 104:13164–13169. doi:10.1073/pnas.0703084104

Schabus M, Dang-Vu T, Heib D, Boly M, Desseilles M, Vandewalle G, Schmidt C, Albouy G, Darsaud A, Gais S, Degueldre C, Balteau E, Phillips C, Luxen A, Maquet P (2012) The fate of incoming stimuli during NREM sleep is determined by spindles and the phase of the slow oscillation. Front Neurol 3:40. doi:10.3389/fneur.2012.00040

Schwartz S, Maquet P (2002) Sleep imaging and the neuro-psychological assessment of dreams. Trends Cogn Sci 6:23–30

Scrima L (1982) Isolated REM sleep facilitates recall of complex associative information. Psychophysiology 19:252–259

Smith C, Weeden K (1990) Post training REMs coincident auditory stimulation enhances memory in humans. Psychiatr J Univ Ottawa 15:85–90

Steriade M (2001) Active neocortical processes during quiescent sleep. Arch Ital Biol 139:37–51

Steriade M (2003) The corticothalamic system in sleep. Front Biosci 8:d878–d899

Steriade M (2005) Grouping of brain rhythms in corticothalamic systems. Neuroscience 137:1087–1106. doi:10.1016/j.neuroscience.2005.10.029

Steriade M, Amzica F (1998) Coalescence of sleep rhythms and their chronology in corticothalamic networks. Sleep Res Online 1:1–10

Steriade M, McCarley RW (1990) Brainstem control of wakefulness and sleep. Plenum, New York

Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A, Balteau E, Dang-Vu TT, Desseilles M, D'Argembeau A, Gais S, Rauchs G, Schabus M, Degueldre C, Luxen A, Collette F, Maquet P (2007) Sleep-related hippocampo-cortical interplay during emotional memory recollection. PLoS Biol 5:e282

Sterpenich V, Albouy G, Darsaud A, Schmidt C, Vandewalle G, Dang VuT, Desseilles M, Phillips C, Degueldre C, Balteau E, Collette F, Luxen A, Maquet P (2009) Sleep promotes the neural reorganization of remote emotional memory. J Neurosci 29:5143–5152. doi:10.1523/JNEUROSCI.0561-09.2009

Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernandez G (2006) Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Nat Acad Sci U.S.A 103:756–761

Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62

Urbain C, Di Vincenzo T, Peigneux P, Van Bogaert P (2011) Is sleep-related consolidation impaired in focal idiopathic epilepsies of childhood? A pilot study. Epilepsy Behav 22:380–384. doi:10.1016/j.yebeh.2011.07.023

Urbain C, Schmitz R, Schmidt C, Cleeremans A, van Bogaert P, Maquet P, Peigneux P (2013) Sleep-dependent neurophysiological processes in implicit sequence learning. J Cogn Neurosci 25:2003–2014. doi:10.1162/jocn_a_00439

van Dongen E, Takashima A, Barth M, Zapp J, Schad L, Paller K, Fernandez G (2012) Memory stabilization with targeted reactivation during human slow-wave sleep. Proc Nat Acad Sci U.S.A 109:10575–10580. doi:10.1073/pnas.1201072109

Walker MP, Stickgold R, Alsop D, Gaab N, Schlaug G (2005a) Sleep-dependent motor memory plasticity in the human brain. Neuroscience 133:911–917

Walker MP, Stickgold R, Jolesz FA, Yoo S-S (2005b) The functional anatomy of sleep-dependent visual skill learning. Cereb Cortex 15:1666–1675

Wang X, Inui K, Qiu Y, Kakigi R (2004) Cortical responses to noxious stimuli during sleep. Neuroscience 128:177–186

Wehrle R, Kaufmann C, Wetter T, Holsboer F, Auer D, Pollmacher T, Czisch M (2007) Functional microstates within human REM sleep: first evidence from fMRI of a thalamo-cortical network specific for phasic REM periods. Eur J Neurosci 25:863–871. doi:10.1111/j.1460-9568.2007.05314.x

Wilson MA, Mcnaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–679

Xie L, Kang H, Xu Q, Chen M, Liao Y, Thiyagarajan M, O'Donnell J, Christensen D, Nicholson C, Iliff J, Takano T, Deane R, Nedergaard M (2013) Sleep drives metabolite clearance from the adult brain. Science 342:373–377. doi:10.1126/science.1241224

Yotsumoto Y, Sasaki Y, Chan P, Vasios C, Bonmassar G, Ito N, Nanez JS, Shimojo S, Watanabe T (2009) Location-specific cortical activation changes during sleep after training for perceptual learning. Curr Biol 19:1278–1282. doi:10.1016/j.cub.2009.06.011

The Role of Sleep in Human Declarative Memory Consolidation

Sara E. Alger, Alexis M. Chambers, Tony Cunningham and Jessica D. Payne

Abstract Through a variety of methods, researchers have begun unraveling the mystery of why humans spend one-third of their lives asleep. Though sleep likely serves multiple functions, it has become clear that the sleeping brain offers an ideal environment for solidifying newly learned information in the brain. Sleep, which comprises a complex collection of brain states, supports the consolidation of many different types of information. It not only promotes learning and memory stabilization, but also memory reorganization that can lead to various forms of insightful behavior. As this chapter will describe, research provides ample support for these crucial cognitive functions of sleep. Focusing on the declarative memory system in humans, we review the literature regarding the benefits of sleep for both neutral and emotionally salient declarative memory. Finally, we discuss the literature regarding the impact of sleep on emotion regulation.

Keywords Declarative memory · Consolidation · Emotion · Memory · Sleep · Emotion regulation

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Contents

1 Introduction

It has become abundantly clear that sleep facilitates the consolidation of declarative information in humans. A wealth of evidence shows that a period of sleep following learning preserves newly acquired knowledge better than a period of wakefulness (see Payne 2011, Stickgold and Walker 2013 for review). While many types of memory are aided by a period of sleep, this chapter will focus exclusively on the impact of sleep on declarative information. Accordingly, our discussion will focus on how various forms of sleep, including nocturnal sleep and napping, as well as sleep deprivation, affect both neutral and emotionally salient declarative memories. First, however, it is necessary to introduce the basics of declarative memory and sleep, as well as the major theories that guide current sleep and memory research.

2 An Overview of the Declarative Memory System in Humans

Declarative memories encompass both episodic and semantic information (Tulving 1985). Episodic memories include the temporal and spatial details of experienced life events or episodes, such as the particular events of your wedding day. Conversely, semantic memories include facts and general knowledge acquired across various life events, but lack details of the exact context in which this information was acquired, such as knowing that Paris is the capital of France. Emotional memories represent a special subclass in the declarative memory domain because, unlike their neutral counterparts, they concern specific events or stimuli that are emotionally salient in nature (Hamann 2001; Kensinger 2009). In this chapter, we use the term "emotional memory" to refer to the processing and storage of this type of emotionally salient information, which evokes feelings of positivity or negativity and often changes arousal. Memories of a first kiss or a horrific car accident are examples of emotional declarative memories, and such information enjoys a privileged status in memory over neutral information due to the cooperation of the neural regions supporting them (Lang et al. 1995; Ochsner 2000). Specifically, neutral declarative memories depend on several medial temporal lobe (MTL) regions, especially the hippocampus (Moscovitch et al. 2005). Damage to this region disrupts the formation of new memories and hinders recall of recently acquired memories that are still hippocampal dependent (Scoville and Milner 1957). Emotional memories are further supported by a complex interplay between these MTL regions and the amygdala, a subcortical structure important for emotional processing (Hamann et al. 1999, 2002; Kensinger and Schacter 2006; McGaugh 2004). Activations of the amygdala have been shown to mediate the effects of epinephrine and cortisol, released during emotional arousal, on structures such as the hippocampus and caudate nucleus (see Fig. 1, McGaugh 2000, 2004). Further, functional interactions between the amygdala and the medial temporal lobe have been shown to predict later memory for emotional information, especially as delays increase between learning and testing (Ritchey et al. 2008). Although memory benefits for emotional over neutral material have been observed after a delay of only minutes (Kensinger and Corkin 2003), it has been suggested that emotion's impact on memory is greatest after a longer delay (i.e., 24 h), likely because such a delay allows consolidation processes to selectively preserve emotional information (Sharot and Yonelinas 2008; Payne and Kensinger 2010 for review). As will be discussed in Sect. 8, sleep during this delay offers a further selective enhancement to these emotionally salient memories (Wagner et al. 2001; Hu et al. 2006; Payne et al. 2008).

Also important to our discussion are the various stages of memory processing. Encoding represents the first stage of the process and encompasses the initial acquisition of new information, which is transformed into mental representations in the brain. The consolidation stage then stabilizes these neural representations over subsequent hours, days, and years, increasing resistance to interference from other

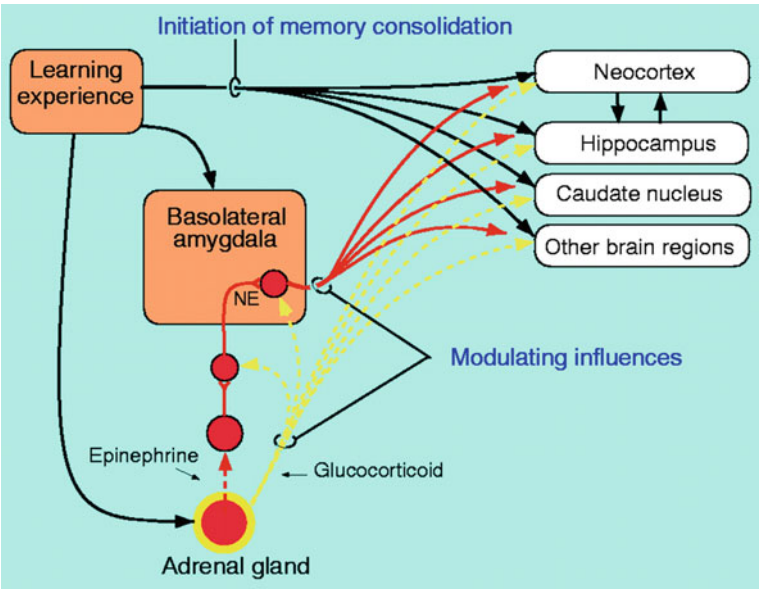

Fig. 1 Neurobiological processes that facilitate the consolidation of memory. A learning experience simultaneously activates time-sensitive storage systems in several brain regions and, particularly if the experience is an emotionally arousing one, activates the release of stress hormones from the adrenal gland and norepinephrine in the basolateral amygdala. The specific brain regions activated are dependent on memory type, and the activity in the amygdala modulates consolidation by affecting the plasticity in other regions (from McGaugh 2000)

competing information. This crucial stage is still not fully understood, with suggestions that it be broken down into substages of stabilization and enhancement (Walker and Stickgold 2006) or that it goes beyond simple stabilization and enhancement to produce qualitative changes in memory representations (for review, see Payne and Kensinger 2010; Payne 2011). The third and final stage is retrieval of the stored memory. Although sleep facilitates the encoding of new memories (Yoo et al. 2007; Van Der Werf et al. 2009) and may smooth the path to effective retrieval, the majority of studies on sleep and declarative memory focus on consolidation, as we do below.

3 Neurochemical and Electrophysiological Properties of Sleep Stages and Their Relationship to Memory Processes

To fully appreciate the body of literature examining the role of sleep in declarative and emotional memory consolidation, it is important to first discuss the properties of sleep itself. Sleep is not a unified, constant state or a period of inactivity. Rather,

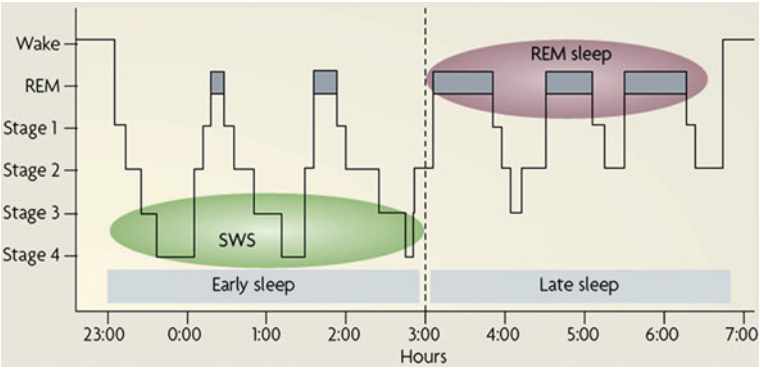

Fig. 2 Slow wave sleep dominates the first half of the night, but during the latter half, REM sleep dominates (from Payne 2011)

it is a dynamic process that progresses through many stages, each with unique neurochemical and electrophysiological properties. As covered in Chap. 1 (Deboer, 2013), sleep is generally delineated as non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is comprised of stages 1–4 as defined by Rechtschaffen and Kales (1968), or more recently redefined by the American Academy of Sleep Medicine (2007) as N1–N3, with each stage defined by specific frequency ranges (see Chap. 1). Collectively, Stages 3 and 4 (or N3) is known as slow-wave sleep (SWS) and represents the deepest sleep state. In a typical night of sleep, the brain progresses through all the stages before beginning the sequence again, repeating this cycle about every 90 min throughout the night. However, the distribution of these stages across a typical night of sleep is not entirely even. The first half of the night contains a majority of the night's SWS, whereas the amount of REM in the second half of the night is nearly doubled from the first (Fig. 2; Payne 2011).

Stage 2, SWS, and REM sleep are most relevant to our discussion on declarative and emotional memory within this chapter, so an understanding of the neurochemical and electrophysiological dynamics within these stages is in order as it serves as the foundation for prominent theories regarding memory processing during sleep (see Sect. 4).

3.1 Non-rapid Eye Movement Stage 2 Sleep

Upon falling asleep, the brain shifts from the waking state, through the Stage 1 transitory state, into Stage 2 sleep. This stage is marked by sleep spindles, high-frequency bursts in the sigma band (12–15 Hz), and K-complexes, brief high-amplitude, negative, high-voltage peaks of approximately 100 μV followed by a slower positive complex and a final negative peak, on background brain activity in

the 5–8 Hz range. Aminergic tone (norepinephrine, NE; serotonin, 5-HT) as well as cholinergic tone (acetylcholine, ACh) are similar to that seen in SWS, both at relatively low levels compared to a waking state (Stickgold et al. 2001; Smith et al. 2004 for review).

Stage 2 sleep spindles can differ in frequency and regions of generation, from slow spindles in the 12–14 Hz range concentrated over frontal locations to fast spindles (14–16 Hz) originating in centro-parietal loci (Sterman et al. 1978; Tanguay et al. 1975; Zeitlhofer et al. 2003). Sleep spindles have been proposed to play a role in reactivating a memory for further synaptic modifications (Rosanova and Ulrich 2005) and implicated in assimilating new and old information (Tamminen et al. 2010). Comparison of baseline spindle activity (quantity and density) to activity following intensive learning has revealed changes that are positively correlated with memory performance on different types of memory tasks, including declarative memory (Gais et al. 2002; Clemens et al. 2005; Schabus et al. 2004).

3.2 Slow-Wave Sleep

As the brain moves into deep NREM sleep or SWS, activity is characterized by high-amplitude, low-frequency oscillations, or delta waves (0.5–4 Hz). Also present are sharp-wave ripples, or fast hippocampal neural oscillations (150–250 Hz), which are grouped by and occur in the transition between the upstates of the slow oscillations (Steriade et al. 1993; De Gennaro and Ferrara 2003; Battaglia et al. 2004; Mölle et al. 2006). These ripples are temporally correlated with sleep spindles (Siapas and Wilson 1998; Sirota et al. 2003) and are a key component in a major theory regarding memory consolidation (Buzsaki et al. 1983; Buzsaki 1989, see Sect. 4). Positron emission tomography (PET) studies have investigated regional cerebral blood flow (rCBF) during SWS and found an overall deactivation of the brain compared to wakefulness, including areas of the midbrain, limbic areas, and higher cortical areas such as the dorsolateral prefrontal cortex (DLPFC; Braun et al. 1997).

Additionally, noradrenergic, serotonergic, and cholinergic connections in the cortex are at low firing levels, with levels of ACh at their very lowest during SWS (less than one-third of that seen during active wake; see Fig. 3). We emphasize the

	Active Wake	Quiet Wake	SWS	REM
ACh	++	+	–	+++
NE 5-HT	++	+	+	–

Fig. 3 Graphical representation of varying concentrations of neuromodulators across a variety of brain states. *ACh* Acetylcholine, *NE* Norepinephrine, *5-HT* Serotonin

role of ACh and NE throughout our description of the sleep stages because these chemicals have been shown to directly affect hippocampal neurons and impact declarative memory traces. High ACh levels benefit the encoding process (during wakefulness) because this neurotransmitter suppresses glutamatergic receptors in the hippocampus, reducing connectivity between the hippocampus and long-term memory stores in the neocortex. This in turn prevents the concurrent reactivation of older, competing memories in the hippocampus and thus minimizes interference. However, reduced ACh levels during SWS facilitate feedback from the hippocampus to the neocortex by releasing most glutamatergic synapses from suppression, thus aiding declarative long-term memory processing and systems consolidation (Hounsgaard 1978; Valentino and Dingledine 1981; Rovira et al. 1983; Hasselmo and Bower 1992; Herreras et al. 1988; Hasselmo 1999; Hasselmo and McGaughy 2004). When levels of ACh are experimentally increased during SWS-rich sleep early in the night, performance on a word associates task, which typically improves following SWS, is weakened (Gais and Born 2004).

Norepinephrine released from the locus coeruleus (LC) during NREM sleep modulates activity in the neocortex and the hippocampus as well (Aston-Jones 2004). Bursts of activity from the LC correlate with sleep spindles and slow oscillations during SWS and may be implicated in memory consolidation (Gais et al. 2011). LC and NE levels have been shown to transiently increase after a period of learning (Eschenko and Sara 2008; Sara 2009). Furthermore, blocking NE activity during NREM sleep with clonidine, but not during wake, results in a reduction in sleep-dependent facilitation of memory (odor recognition), while an NE reuptake inhibitor increased memory consolidation (Gais et al. 2011).

3.3 Rapid Eye Movement Sleep

While the literature heavily implicates SWS as the most critical stage for declarative memory consolidation, there is a growing body of evidence suggesting that REM sleep may selectively facilitate emotional declarative memories (see Sect. 8). As the brain shifts into REM sleep, characterized by a drastic reduction in muscle tone and low-amplitude, high-frequency EEG patterns (tonic events of REM sleep), as well as periodic rapid eye movements (REMs) and muscles twitches (the phasic events of REM sleep) (Carskadon and Dement 1989), levels of brain activation are generally comparable or even greater than that seen during wakefulness, especially in the brainstem, basal ganglia, hippocampus, nearby limbic areas, and some cortical areas. Specifically, increased activity between amygdala, hippocampus, and cortical areas such as the mPFC (Braun et al. 1997), which are important emotional centers of the brain, points to REM as a possible ideal stage for emotional memory consolidation (Maquet et al. 1996). Further, noradrenergic connections in the cortex are virtually silent and ACh levels are about 60 % lower than in the waking state (though, see Vazquez and Baghdoyan 2001). However, in the hippocampus and surrounding regions, ACh levels are elevated above those seen during waking

(Hasselmo 1999). The resulting suppression of glutamatergic receptors may again shut down the flow of information from the hippocampus to the neocortex (Hasselmo 1999), perhaps facilitating cortico–cortico interactions (Payne et al. 2004; Payne 2011). ACh elevations have also been associated with the promotion of emotional memory during REM sleep, particularly given that ACh activation in the amygdala is associated with memory enhancing effects (McGaugh 2004).

4 Theories of Sleep and Declarative Memory Processing

To fully appreciate the research that will be discussed below, we first outline the basic theories used to motivate experiments and interpret results. Sleep and declarative memory research is generally understood within two theoretical frameworks, which are based upon the neurochemical and electrophysiological properties of SWS. According to the standard two-stage theory of consolidation (Buzsaki et al. 1983; Buzsaki 1989; McClelland et al. 1995), the first stage begins with rapid encoding of new information through waking interaction with the environment. Experience initiates a flow of activation from sensory receptors, through thalamic weigh stations (with the exception of olfactory processing) to the entorhinal cortex and input layers of the CA3 region of the hippocampus, both directly and indirectly through the dentate gyrus (Chrobak and Buzsaki 1994). As described above, the high levels of ACh during the waking state facilitate this process. Subsequently, during SWS, sharp-wave ripples participate in the reactivation of neuronal networks that were most recently fired during waking, namely those representing declarative information (Pavlides and Winson 1989; Wilson and McNaughton 1994; Skaggs and McNaughton 1996; Kudrimoti et al. 1999; Nadasdy et al. 1999; Maquet et al. 2000; Louie and Wilson 2001; Hoffman and McNaughton 2002; Ji and Wilson 2007). Best demonstrated in an animal study by Wilson and McNaughton (1994), reactivation of waking neuronal activity was found to occur primarily during SWS. They examined neuronal firing patterns of place cells in the hippocampi of rats exploring an environment prior to sleep and then observed a "replay" of this activity in a time-compressed manner during SWS (however, see Hennevin et al. 2007, for a critique). This replay is thought to lead to long-term potentiation (LTP), the predominant candidate as a mechanistic explanation for synaptic consolidation within a network (Sirota et al. 2003; Brehens et al. 2005; Whitlock et al. 2006; Diba and Buzsaki 2007).

LTP is initiated by the tetanic stimulation of one neuron (the presynaptic neuron), which binds glutamate to the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) subtype receptors of the postsynaptic neuron and causing depolarization. Prolonged depolarization causes the magnesium block in the N-methyl-D-aspartic (NMDA) subtype glutamate receptors to be removed, allowing calcium influx and beginning a second messenger cascade resulting in activated kinases, gene transcription, and protein synthesis (Sweatt 1999; LeDoux 2002). The result of this process is an increase in surface AMPA and NMDA receptors at the

synapses involved in firing the cell, dendritic growth, increased channel conductance in the postsynaptic cell, and growth of new terminal branches and synapses in the presynaptic cell. All of these changes due to LTP strengthen the connection between the two cells, making them more likely to fire together in the future (Bliss and Lomo 1973). Essentially, when a presynaptic cell takes part in firing a postsynaptic cell, they both benefit from the processes described above, becoming "wired together," increasing the chances they will fire together again in subsequent activations, similar to the reactivation seen during SWS (Hebb 1949). The strength of the bursts of sharp-wave ripples during SWS is sufficient to induce LTP within the network (Buzsaki 1989) and some evidence ascribes a causal role to sharp-wave ripples in memory consolidation (O'Neill et al. 2010). Selective suppression of sharp-wave ripples in rats previously trained on a spatial task resulted in significant performance impairments during retesting, although it has not been determined whether the absence of ripples or disruption of neuronal replay during SWS is the exact cause of the impairment (Girardeau et al. 2009; Ego-Stengel and Wilson 2010).

An alternate theory proposed by Tononi and Cirelli (2003, 2006) ascribes an indirect role of SWS in memory processing. This theory is based on the observation that synapses are continuously potentiated through the waking hours, mostly with everyday activities but specifically with focused learning, thus depleting synaptic resources and increasing the threshold for neuronal firing. Coupled with this observation is a homeostatic increase in the need for SWS, so that as the need increases, more SWS is obtained at sleep onset, gradually decreasing over the sleeping period. According to this theory, SWS serves to globally downscale, or reduce synaptic weights, bringing them back to baseline levels so that plasticity and thus the ability to take on new information is restored. This downscaling is a result of the alternating synchronous hyper- and depolarization that occurs in cortical circuits during SWS, with the changes in membrane potential serving to reset the synaptic strengths. Regionally specific or "local" increases in slow-wave activity have been shown to correlate with the location of activation during intensive learning, so that SWS can locally and globally return the brain to baseline (Huber et al. 2004). According to this theory, memory is therefore a by-product of the active downscaling that occurs during SWS. Although there is global downscaling of synaptic strength, the synapses involved in a learned memory trace are stronger than those involved in firing during everyday waking experience. As the latter falls below threshold for firing, the memory trace stands out in an increase of the signal to noise ratio. However, it is unclear whether downscaling benefits memory by occurring in the hippocampus proper, which has conflictingly been shown to maintain firing rate over time (Buzsaki et al. 2002), or only the cortical areas potentiated by learning and associated with the memory trace.

These two theories regarding the role of SWS in declarative memory processing are not mutually exclusive, as both processes could occur simultaneously, with consolidation from the hippocampus to the neocortex happening in conjunction with global downscaling to reset the brain. Keeping these theories in mind, we will next detail the research demonstrating superior memory and refined neural network

activity reflecting systems consolidation after overnight sleep and daytime naps (Sects. 5 and 6), and the deleterious effects of sleep deprivation (Sect. 7) on memory for both neutral and emotionally salient information (Sect. 8).

5 Overnight Sleep Benefits Declarative Memory

5.1 Roles for Sleep in Memory Consolidation

While it has been established that sleep promotes the consolidation of newly acquired memories, the true nature of the function of sleep in such processing continues to be disputed. Three possible roles (*passive, permission, and active*) have been suggested to describe the impact of sleep on memory consolidation (Ellenbogen et al. 2006), each with different proponents. The first role has been deemed the *passive* theory, which, as demonstrated by the conclusions drawn from early studies such as those conducted by Heine (1914) and Jenkins and Dallenbach (1924), posits that memories benefit from a period of sleep simply due to shielding from "the interference, inhibition, or obliteration of the old by the new" (Jenkins and Dallenbach 1924, p. 612). Essentially, this theory contends that sleep merely offers protection from the influence of new incoming information and thus protects recently learned information from the effects of interference for the duration of sleep (Wixted 2004; Vertes and Siegel 2005), with the memory once again susceptible to interference upon awakening.

The *permissive* hypothesis (Ellenbogen et al. 2006) similarly claims that sleep shields new memories by offering an opportunity for reduced interference, but it further asserts that this opportunity is only valuable if it occurs within a certain time frame following learning. Consolidation occurs during both sleep and wakefulness; however, sleep offers greater consolidation efficiency because of the reduction of interference during this state. Importantly, this effect of sleep is time sensitive, such that sleep must occur during a period in which the memory is still labile, prior to the stabilizing effects of gene expression and synaptic modifications, in order to have any consolidation benefit.

Conversely, the *active* hypothesis (Ellenbogen et al. 2006) posits that sleep actively facilitates memory consolidation, rather than simply protects newly learned information from interference. Unlike the previous two hypotheses, this theory stresses the importance of the unique neurochemical environment and physiological events of sleep, such as sharp-wave ripples and sleep spindles discussed earlier (see Sect. 3), for the successful consolidation of memory. A growing body of evidence supports such an active role, with research revealing changes in hippocampal activation and reorganization of brain circuitry after sleep, as well as changes in spindle density and slow-wave activity following learning. For the purposes of this chapter, the *active* hypothesis is most widely represented, with most discussions and reviews reflecting support for the claims of this premise.

5.2 Behavioral Evidence for an Active Role of Sleep in Memory Formation

Early support for the active hypothesis examined the contribution of particular stages of sleep over wakefulness in later declarative memory performance. Using a word-pair learning paradigm, one such study manipulated which portion of the sleep period, or an equivalent period of wake, occurred during a consolidation delay following learning (Plihal and Born 1997). Given the cyclic nature of sleep and the varying distributions of SWS and REM across the night, requiring participants to memorize word pairs prior to bedtime and sleep only for the first half of the night prior to testing ensured that the intervening sleep contained mostly SWS. Alternatively, requiring participants to sleep the first half of the night prior to learning and sleep again for the second half of the night before being awakened and tested ensured that more REM was obtained during the intervening sleep. Results confirmed that participants in the early-sleep group obtained more SWS than the late-sleep group, while the late-sleep group obtained more REM than the early-sleep group, with equivalent amounts of Stages 1 and 2 obtained between the groups. Crucially, a period of sleep improved recall of previously learned word pairs above wakefulness, but only when sleep occurred over the first half of the night, or the "early"-sleep opportunity that was rich in SWS. Because this study indicated a role for this specific stage, rather than a period of sleep in general, it strongly suggested that sleep actively promoted learning instead of simply protecting newly learned information from interference.

This "early-/late"-sleep paradigm, while not an ideal design to address potential circadian confounds, has been subsequently used to implicate active sleep processes in other types of declarative memory consolidation and modulation of physiological reactivity as well. Like episodic memories for pairs of words, spatial memories also rely on functioning of the hippocampus. This type of memory includes mental rotation tasks, such as those that require remembering placements of objects in an imaginary scene after it has been rotated from the original viewing angle (Plihal and Born 1999b). After early sleep, locating object placements in this task is more accurate than after late sleep or wake, again indicating a role for SWS. Aside from the implication of active sleep-based learning processes, investigations such as these were pivotal to establishing an association between SWS and declarative learning tasks. Although such a relationship may be oversimplified, it has survived more stringent physiological testing for certain memory types.

5.3 Physiological Evidence for an Active Role of Sleep in Memory Formation

Physiological evidence has also offered support for an active role for sleep in memory consolidation. Orban et al. (2006) demonstrated, using fMRI, increased striatal activity and changes in functional connectivity between the striatum and

hippocampus, positively correlated with performance on a virtual navigation task after regular sleep versus sleep deprivation (discussed further in Sect. 7.3). The authors conclude that the covert shift in activity from hippocampus-dependent activation to striatal control reflects sleep-dependent consolidation processes. Similarly, Payne and Kensinger (2011) demonstrated a more consolidated pattern of activity for emotional memory after a night of sleep versus daytime wakefulness (discussed further in Sect. 8.1). Physiological evidence also demonstrates a SWS-declarative memory connection. Learning a virtual navigation task has been shown to increase activation, via cerebral regional blood flow (rCBF), of the right hippocampus and parahippocampal region during subsequent NREM sleep, primarily during SWS. This increase was also associated with increased performance on the task following sleep (Peigneux et al. 2004). Importantly, those who did not learn this task prior to sleep did not display the same neural activity increases in these regions, indicating that this change in brain physiology during SWS possibly resulted from the processing of this learned information. Further, reintroducing cues from a learning episode, such as an odor originally presented during the encoding of an object–location pairing task, during subsequent SWS has been shown to increase hippocampal activity during this stage, as well as lead to improved post-sleep memory for the learned material; presenting the odor during REM sleep or wake showed no such benefit (Rasch et al. 2007). Research designed to manipulate slow waves directly, increasing slow-wave activity through transcranial direct current stimulation (Marshall et al. 2004, 2006) or suppressing them with auditory tones (Van Der Werf et al. 2009), respectively, improves and impairs performance on declarative memory tasks. Finally, several studies have demonstrated increased hippocampal sharp-wave ripples during SWS after a period of learning, which were correlated with successful subsequent retrieval (Eschenko et al. 2008; Ramadan et al. 2009). Such physiological evidence compliments previous behavioral studies to support the hypothesis of active processing occurring during sleep and further suggests a SWS-specific mechanism involving activations of the hippocampus to promote declarative learning.

Several studies have demonstrated functional changes in Stage 2 sleep parameters that potentially implicate this stage in declarative memory processing as well, adding support to an active role for NREM sleep in processing of neutral declarative memories (Gais et al. 2002; Clemens et al. 2005; Schabus et al. 2004). In these experiments, subjects' average, normal sleep spindle density (i.e., the number of 12–16 Hz bursts of activity within Stage 2 sleep per 30 s epoch), measured either during baseline sleep (Clemens et al. 2005) or during sleep following a non-learning control task (Gais et al. 2002; Schabus et al. 2004), was found to significantly increase during sleep directly following a period of intensive learning. Only those participants who showed an increase in spindle density during post-learning sleep demonstrate improved memory performance (Schabus et al. 2004). Sleep spindles have similarly been found to increase during SWS after an intensive learning session (Eschenko et al. 2006). As mentioned earlier, spindles are temporally correlated with sharp-wave ripples (Siapas and Wilson 1998; Sirota et al. 2003) as well as slow

oscillations (Steriade and Timofeev 2003; Mölle et al. 2009) and can be considered plastic events themselves (Rosanova and Ulrich 2005). Therefore, it is not surprising that they play a role in declarative memory processing.

5.4 Memory After Extended Consolidation Delay Designs

Despite such mounting evidence, some continue to dispute the active hypothesis due to the unequal amounts of time that participants in sleep and wake conditions are subjected to waking interference. This is particularly problematic in designs where performance after an 8- to 12-h delay of daytime wakefulness (where subjects are continually exposed to everyday interfering input) is compared to an 8- to 12-h delay of nocturnal sleep (where a majority of the delay is spent asleep and thus provides protection from interfering stimuli; e.g., Payne et al. 2009; Wagner et al. 2004). To address this issue, recent studies have utilized extended consolidation delays (i.e., 24 h) that allow all participants to receive equal amounts of wakefulness and sleep, with only the timing of sleep varying between groups. As an example, Payne et al. (2012a) tested memory for pairs of semantically related or unrelated words following four different delay intervals. As in previous studies (Payne et al. 2009; Wagner et al. 2004), a 12-h delay following training in the morning or evening allowed for a period of daytime wake or nocturnal sleep during the consolidation period. However, a 24-h delay allowed either a period of wake followed by sleep (wake-first group) or a period of sleep followed by wake (sleep-first group). While both 12-h groups retained an equal number of the related word pairs, those receiving a period of sleep during this delay had better memory for the unrelated word pairs than those who remained awake. This finding alone provides initial evidence against an interference account, as memory for both related and unrelated word pairs would have been impacted similarly by sleep if its effect was to generally shield information from everyday normal waking interference, as predicted by the passive theory.

Further, comparison to the 24-h groups revealed that forgetting of these word pairs was doubled over the waking period when wake came prior to sleep as opposed to following sleep, while forgetting over the sleep period remained the same regardless of its placement in the 24-h delay. Similarly, Talamini et al. (2008) found that sleep not only protected memory for face–location pairings over wakefulness, but also reduced forgetting occurring during the waking portion of a 24-h delay when sleep occurred prior to wakefulness as opposed to following it (see Fig. 4). Given an interference account, the amount forgotten over the portion of the delay filled with wakefulness in these two studies would be the same regardless of its position to sleep. The fact that forgetting was reduced when learning was closely followed by sleep suggests that sleeping actively stabilizes newly acquired memories, which are then more resistant to interference during subsequent waking (Payne et al. 2012a).

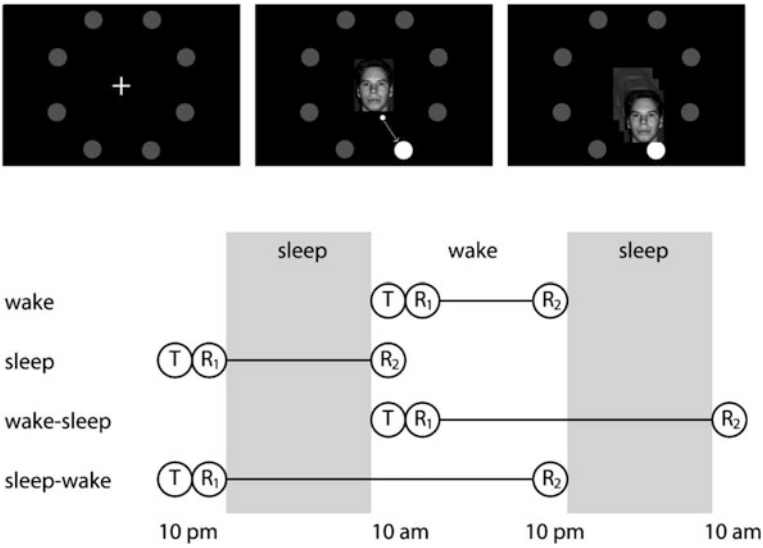

Fig. 4 The design used by Talamini et al. (2008). Participants were first trained to pair faces with spatial locations and were later tested on their memory for these pairings across delays varying in the positioning of sleep

Such extended delays have not only been utilized to rule out interference accounts, but have also provided evidence that sleep may act to restore degraded memories. For example, Backhaus et al. (2007) examined memory for word pairs in children after both a 12-h delay as well as a 24-h delay. Children either initially learned word pairs in the evening and obtained a night of sleep prior to a memory test the following morning (12-h test) as well as the following evening (24-h test) or learned the word pairs in the morning and obtained wakefulness during the day prior to testing that evening (12-h test) as well as the following morning (24-h test). Performance at the 12-h test was better when it followed sleep rather than wake. Further, performance at the 24-h test revealed that when wake followed sleep, memory did not change over the waking interval, remaining at levels seen at initial testing following sleep. This result contributes to the evidence of the active stabilization provided by sleep, which protects the memory from the effects of subsequent interference and decay incurred during wake. Interestingly, performance at the 12-h test, which was worse in those who obtained a day of wakefulness prior to sleep, *improved* at the 24-h test following the subsequent overnight sleep interval (see Fig. 5). Coupled with studies revealing a similar rejuvenating effect when sleep follows a degrading period of wakefulness within a 24-h time span (Fenn et al. 2003), this finding implicates an active restoration of memory by sleep, allowing one to recover a previously decayed memory in some cases.

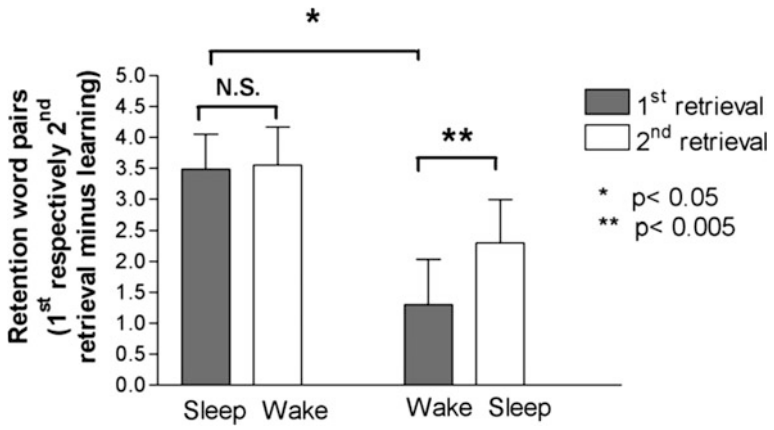

Fig. 5 Children who were trained on word pairs showed no boost in subsequent memory performance when a sleep period came prior to a wake period 24 h later, but when the waking interval proceeded a period of sleep, memory improved at a 24-h test. These results suggest that not only does sleep strengthen memory traces against later interference, but may also play an active role in improving memory (from Backhaus et al. 2007)

5.5 Insight, Gist, and Rule Extraction with Sleep

Because of its role in memory consolidation, sleep is also believed to play an important role in problem solving, supporting the strategic combination of information and experiences from daily life into a useful solution during sleep. Indeed, there are many examples of "sleeping on a problem," including groundbreaking solutions to some of science's most perplexing problems arriving through a night of sleep. Without these sleep-induced breakthroughs, we might not know the chemical structure of benzene or have the perfect organization of the periodic table of elements (Stickgold and Walker 2004). Beyond these popular anecdotes, some empirical evidence has begun to surface. Recent studies suggest that the benefit of sleep to memory goes beyond stabilization and enhancement of new knowledge in its veridical form, to restructure and transform that knowledge in a manner that allows for its flexible use (see Payne 2011; Stickgold and Walker 2013 for review). For example, sleep helps modify memories so that inferences can be made (Ellenbogen et al. 2007), insights can be achieved (Wagner et al. 2004), rules and meaning can be extracted (Payne et al. 2009), and complex problems can be solved (Stickgold and Walker 2013).

In one such study, Wagner et al. (2004) found that sleep as opposed to wakefulness was more likely to induce the discovery of a shortcut in a number reduction task. On each of several trials, participants were to reduce a string of eight numbers into a string of seven, given a rule for reducing two of these original numbers at a time. The goal was to find the identity of the last number in the new string. What the participants did not know was that there was a hidden shortcut to obtaining this final

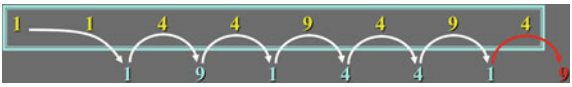

Fig. 6 A visual depiction of the number reduction task. Wagner et al. (2004) taught participants to solve puzzles composed of three digits (in this case 1's, 4's, and 9's). Starting from the *left* side, if the numbers are the same, they enter that number (here, the first two numbers are 1's, so the participant enters that number). If the numbers are different, they enter the third number possible. They then compare each new number to the next number in the sequence until they reach the final number (in *red*). Unknown to the subjects, embedded in this task is a hidden shortcut that can be used to speed performance; the last three numbers are always a mirror image of the prior three numbers, with the first number of the mirror (in this case, 9) always being the same as the final answer (Stickgold and Ellenbogen 2008)

number faster; the last three numbers of the new string were actually a mirror image of the previous three, so that once the participant found the second number in the new string, he or she would also know the last number in the string (see Fig. 6). Wagner et al. (2004) had participants undergo an 8-h delay containing nocturnal sleep, nocturnal wakefulness, or daytime wakefulness after training on this task. They found that those who slept after learning were twice as likely as those who stayed awake to find the hidden solution to this task during subsequent testing. Further, even those who did not discover the hidden shortcut benefited from an increased speed of rote responding in the sleep group, a result not found for those in the wake group. Subsequent studies have shown the benefit of sleep to similar rule-dependent memory paradigms as well, such as tasks relying on probabilistic learning of artificial grammars (Fischer et al. 2006) or musical sequences, which appear to depend on the amount of SWS obtained during a period of sleep (Durrant et al. 2011). This evidence suggests that sleep offers an advantage to problem solving after an initial introduction to the problem, an advantage that likely results from the reorganization of memory traces during sleep (Wagner et al. 2004).

Another study examined the role of sleep in enhancing relational memory or the ability to flexibly generalize across existing stores of information. In their study, Ellenbogen et al. (2007) had participants intentionally encode abstract shapes that represented five "premise pairs" (A > B, B > C, C > D, D > E, and E > F). Unknown to the subjects, however, these pairs fit within a larger hierarchy (A > B>C > D>E > F). After a delay of 20 min, 12 h of wake, 12 h of sleep, or 24 h, subjects were tested on not only the premise pairs, which provided the building blocks of the hierarchy (e.g. A > B, B > C, etc.), but also for novel "inference pairs" that had not been previously studied (e.g., B > D, C > E, B > E, etc.; see Fig. 7). The question was whether subjects would be able to correctly infer these relationships without the benefit of direct experience. At retest, all four groups showed nearly identical premise pair retention, but a prominent separation was clear in their abilities to make relational inference judgments. Those in the 20-min group were unable to make the correct inference judgments, with performance nearly at chance. Those in the 12- and 24-h groups displayed a significant improvement in relational memory, but the most striking contrast was the difference in performance between

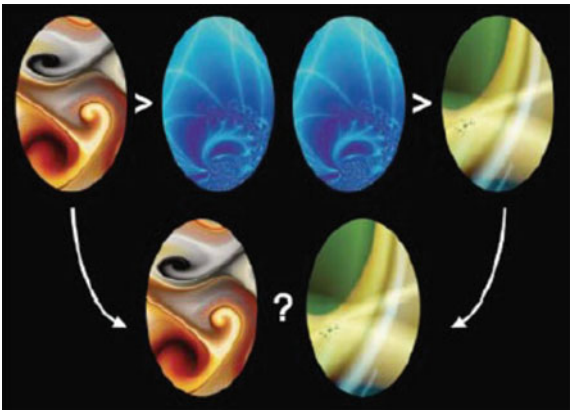

Fig. 7 Example stimuli from Ellenbogen et al. (2007). Through multiple trials, participants learned individual "premise pairs," for example that the abstract shape with the orange hue is greater than the blue and that the blue is greater than the green. After a delay, they were asked to make inferences about pairings that had never been seen before, yet conformed to the hierarchy (*orange* > *blue* > *green*). The question is whether subjects would be able to correctly infer that the orange shape was greater than the green. Sleeping prior to testing triggered a significant boost in inferential ability (Stickgold and Ellenbogen 2008)

the 12-h period containing sleep compared to the 12-h period of wake. Participants in the sleep group were better at making the most distant, and arguably difficult, inferential judgment (the B > E pair) than the group that remained awake, yet this increase in performance did not correlate with an increase in subjective confidence. This provides evidence that sleep facilitates human inferential ability by enhancing relational memory binding and, further, that this process may occur at an unconscious level (Ellenbogen et al. 2007).

Sleep has also been implicated in the ability to extract meaning or "gist" from previously learned information. A study by Payne et al. (2009) utilized the Deese-Roediger-McDermott (DRM) paradigm, which requires participants to aurally encode lists of words for a later memory test. Each of these lists is composed of words that are semantically related to an unpresented theme or gist word that is commonly falsely recalled as having been included in the original list (e.g., "nurse," "needle," and "hospital" are a subset of the studied words that appear on the list for the unpresented gist word "doctor"; Roediger and McDermott 1995). At recall, subjects were asked to record as many words as they could remember hearing. While memory for studied words decreased across delays that included both wake and sleep, the gist words were more often remembered after sleep, showing a numerical improvement. Payne et al. (2009) verified this preferential role for sleep in gist memory in a follow-up nap study. Interestingly, despite previous evidence associating SWS with improved declarative memory performance (Peigneux et al. 2004; Rasch et al. 2007), Payne and colleagues found an inverse relationship between memory for the previously presented words and SWS. Given the semantic

relatedness of the words on the studied lists, it was suggested that while SWS may be key for episodic and spatial memory Consolidation (Plihal and Born 1997), it might actually impede semantic memory consolidation. Although it may seem counterintuitive that sleep would promote false memory for gist, this may be a case of sleep rendering memories less accurate but also more useful (a case of seeing the forest through the trees).

6 Memory Consolidation During Daytime Naps

A recent surge in memory research implementing daytime naps not only serves to replicate the results of overnight studies, but also to achieve more insight into the way sleep stages facilitate memory. Naps are used both as a more economic approach to sleep and memory research (because they are typically shorter and therefore cost less), as well as to address inherent confounds that arise in overnight sleep designs. Naps help control time-of-day confounds, with equivalent times of training and testing between groups who sleep and remain awake without the confounds associated with sleep deprivation (see Sect. 7). Additionally, naps minimize concerns about circadian confounds inherent in designs that compare performance in overnight sleep groups to daytime wake groups, which can only be controlled to a certain degree by testing performance across short delays in the morning and evening in typical circadian control groups (e.g., Payne et al. 2008, 2009). While the overnight designs have their own merit as discussed earlier (Sect. 5), nap designs are increasingly employed to practically address the issues stated above and are of sufficient length to differentiate performance between sleep and wake groups, replicating findings from overnight studies.

Due to the typical length of naps in most studies (60–90 min), the potential contributions of particular stages to memory can also be more carefully isolated than in the "early-/late"-sleep paradigm described above (Plihal and Born 1999a, b). This is because a 60- to 90-min nap generally includes Stage 1, Stage 2, and SWS, but little, if any REM sleep. Thus, it is possible to assess only the contribution of NREM sleep to memory consolidation. Using this method, Tucker et al. (2006) found improved paired-associate memory after a nap only containing NREM sleep, but no benefit for a procedural mirror-tracing task. Takashima et al. (2006) additionally found a significant positive correlation between the amount of SWS obtained in a 90-min nap and recognition of pictures viewed before sleep. They also found a negative correlation between memory and hippocampal activation, a finding that grew stronger over a period of 30 days and implicated superior long-term consolidation from the hippocampus to the neocortex after obtaining SWS. Using a virtual maze-learning task, Wamsley et al. (2010) found a positive correlation between dream imagery reported from NREM sleep during a nap and post-nap performance, reflective of processing occurring during the nap. Further, Schmidt et al. (2006) saw increases in spindle density and spectral power in the spindle frequency range after learning difficult paired-associates, compared to easily

learned pairs, positively correlating with better post-nap performance. Similarly, Tucker and Fishbein (2008) only saw improvement after a NREM daytime nap when the learned material was strongly encoded during task acquisition, suggesting that the sleeping brain preferentially processes information that perhaps required more neural resources to learn, leading to stronger synaptic connections and potentially higher probability of reactivation during NREM sleep.

6.1 How Much Sleep is Necessary for Memory Consolidation?

The type of sleep obtained during different nap lengths can also be investigated during daytime sleep without incurring sleep deprivation effects as would be found when manipulating overnight sleep duration. A 2008 study by Lahl et al. found that a brief period of sleep of as little as 6 min facilitated superior recall of a learned list of words compared to remaining awake, but this effect was not as effective as obtaining a nap of 35 min. As a follow-up to this study, Alger et al. (2012) similarly had groups that either achieved a brief nap (10-min), a longer nap (60-min), or remained awake, comparing performance using a bimodal paired-associates task (words paired with sounds). In this study, the findings of Lahl et al. were replicated in that a test of memory for paired-associates immediately after the nap/wake retention period revealed a benefit to performance in the two nap groups, with the longer nap facilitating the memory more than the shorter nap, compared to remaining awake. However, the brief nap's benefit was found to be temporary and not indicative of true memory stabilization after a stimuli-related interference task was introduced directly following the initial memory test. Memory for the paired-associates degraded in the 10-min nap group, subject to forgetting after interference, while the longer nap group's memory was relatively protected and preserved. These benefits were seen to persist over a week retention period in the longer nap group, compared to the 10-min nap and wake groups, whose memory decayed similarly. Taking these findings together, it becomes apparent that a nap must include SWS, as opposed to only containing Stages 1 and 2 in the brief 6- and 10-min naps, in order to protect and begin to consolidate the declarative memory trace. In fact, similar results from Schabus et al. (2005) using paired-associates and cued recall performance found that only nappers who obtained SWS during a 60-min nap opportunity showed improvement in the declarative task, compared to those who only had Stages 1 and 2 sleep.

6.2 Naps Facilitate Selective Consolidation

Naps have not only been shown to facilitate veridical memory consolidation, but also to promote preferential memory consolidation, gist extraction, and insight. Saletin et al. (2011) utilized a directed forgetting/remembering paradigm in which

an explicit direction of "R" to remember or "F" to forget was given after every presented item. Baseline recognition testing found similar memory performance for cued-to-remember items and cued-to-forget items between groups. However, a nap opportunity of 100 min led to significant selective enhancement of the "remember" items, compared to the wake group, but not for the "forget" items. Similarly, emotional information, compared to neutral, is selectively consolidated during naps. For example, naps have been shown to boost memory for emotional scenes in their entirety (Nishida et al. 2009), as well as memory for specific components of emotional scenes (objects versus associated backgrounds; Payne et al., submitted, see Sect. 8).

Naps can also promote gist extraction, with subjects recalling words that were not actually present in a studied word list, but that represent the general theme or gist of the list. Payne et al. (2009) were able to replicate the extraction of gist found in an overnight design using the DRM task, described earlier, with a 90-min daytime nap. As in the overnight study, they found a significant negative correlation with SWS, concluding that the ability to extract the gist of a list requires the recognition that all the words are related, drawing upon access to semantic memory stores that may not depend on SWS and may in fact be inhibited by it (Payne et al. 2009).

Work by Lau et al. (2010, 2011) has explored relational memory using daytime naps. In a 2010 paper, Lau et al. used an associative inference task in which faces were paired with objects such that one face (A) would be paired with an object (B) in one trial, while the same object (B) was paired with another face (C) in a second trial. After a retention period containing either a nap or wake, those who slept not only preserved the direct AB and BC pairs of faces and objects significantly better than those who remained awake, but also formed superior indirect relational memory of the two faces associated with the same target object (AC pair), similar to relational memory enhancements seen after a full night of sleep (Ellenbogen et al. 2007). In 2011, Lau et al. presented subjects with Chinese characters, which could be grouped by characters containing the same radical or component of the character with a shared semantic component among the group (characters for "mother" or "sister" with the same radical meaning "female"). After a nap, versus no nap, subjects were better able to correctly guess the meaning of a newly presented character with a shared radical of one of the originally learned groups of characters, as well as explicitly state the meaning of a radical. Interestingly, the superior ability to extract this implicit rule was better after sleep regardless of whether the nap occurred immediately after the learning session or a couple hours later.

6.3 Placement of the Nap in Time Impacts Memory Consolidation

It is still relatively unknown whether naps of equal length occurring at different times throughout the day facilitate memory similarly. It is well established that as the time awake during the day progresses, levels of adenosine build up, increasing

the need for SWS, so that later naps contain higher proportions of SWS compared to Stage 2 or REM sleep (Porkka-Heiskanen et al. 1997; Retey et al. 2005). Conversely, REM sleep follows a circadian cycle, so that naps early in the day contain more REM sleep than SWS (Webb et al. 1966; Karacan et al. 1970). There is also evidence for a shift in the amount of Stage 2 sleep obtained throughout the day in conjunction with the shifts in other stages. It stands to reason that a shift in the type of sleep achieved during a nap may impact consolidation of declarative information, yet literature regarding this question is deficient and conflicting.

Schoen and Badia (1984) trained subjects on meaningful (short stories) and non-meaningful (nonsense syllables) verbal material and gave them a 2-h sleep opportunity, either at 7 am or at 3 pm, to examine time-of-day effects as well as attempt to elucidate the contributions of sleep stages by taking advantage of the inverse relationship between REM sleep and SWS. However, regardless of the nap time, with testing occurring shortly after the end of the nap sessions, all subjects who napped showed better recall for both types of information than those who remained awake. In conflict with these findings, Alger et al. (2010) trained all subjects at the same time of day on a declarative visual recognition task and had groups of subjects who either remained awake or took a 90-min nap immediately, 2 h, or 4 h after learning, followed by a memory test for the material at 6 pm. Contrary to expected results, the group with the greatest delay (4 h) between training and testing performed significantly better. Interestingly, these subjects also had the greatest amount of SWS during the nap, nearly significantly more than the immediate nap group, reflecting the increase in SWS need as the day progresses and suggesting a critical role for SWS in processing this information.

It still remains to be seen whether placement of the nap throughout the day to manipulate the type of sleep achieved can be used to reveal contributions of specific sleep stages, particularly when holding constant the time of training and testing between groups. However, naps do remain an excellent method of attempting to tease out roles for sleep stages in memory consolidation, if such discrete contributions occur, or to determine possible sequential processing during sleep, without the confounds of sleep deprivation or more pronounced circadian differences.

7 Sleep Deprivation Impairment of Declarative Memory

While the above sections have discussed how either an overnight or daytime period of sleep benefit declarative memory, it is also essential to review how sleep deprivation hinders memory, as it informs about the mechanisms upon which sleep and memory hypotheses are built. Both animal and human studies have shown the impairment of newly learned information by partial or total sleep deprivation, leading to a subsequent decline in performance compared to control groups (Peigneux et al. 2001; Gais et al. 2006; Ferrara et al. 2006) or even the creation of false memories (Diekelmann et al. 2008).

As one example, in a study by Gais et al. (2006) using a four-group design, two groups learned in the morning and two more learned in the evening and were tested either 24 or 36 h later. The groups learning in the morning had a higher rate of forgetting compared to those who slept soon after learning, even though the groups had similar waking retention times. To follow up, they also tested two more groups, both of whom learned in the evening, one sleeping immediately after while the other was sleep deprived throughout the night but then allowed to sleep the next morning. After another recovery night of sleep, 48 h after learning the sleep deprivation group showed significant forgetting compared to the control group. Importantly, the 24-h (8–8 am) and 36-h (8 pm–8 am) groups described above had the same amount of waking retention time, confirming that there is a window of time soon after learning that is critical for memories to stabilize during sleep (see also Payne et al. 2012a).

7.1 The Effects of Sleep Deprivation at the Cellular Level

The effects of sleep deprivation at the behavioral level may not be surprising when one considers the marked effects of sleep deprivation at the cellular level. Sleep deprivation has been shown to affect neuronal excitability, protein synthesis, and neurochemical transmission, among other processes. Extended sleep deprivation has been reliably shown to impair the ability to produce LTP (Vecsey et al. 2009). As mentioned, under normal conditions, LTP leads to rapid insertion of AMPA and NMDA receptor (NMDAR) subunits on the surface to facilitate faster binding the next time the cell is activated (Sweatt 1999; LeDoux 2002). Prolonged sleep deprivation results in a reduction of surface subunits, insufficient calcium influx during stimulation, and a corresponding decrease in NMDAR-mediated excitatory postsynaptic potentials, concomitant with a significant decrease in performance (Chen et al. 2006). A reduction of LTP has been seen in various regions of the hippocampus, although not in the dentate gyrus (McDermott et al. 2003, 2006).

Sleep deprivation also modulates elements in second messenger pathways (Yang et al. 2008). Vecsey et al. (2009) demonstrated that 5 h of sleep deprivation in mice impaired cyclic AMP (cAMP) and protein kinase A (PKA) signaling through increases in key enzymes, phosphodiesterases (PDEs), responsible for breaking down cAMP. Consequently, this type of alteration of normal functioning results in disruption of gene transcription and protein synthesis, impaired consolidation of learned tasks, and later performance (Graves et al. 2003; Vecsey et al. 2009). However, sleep deprivation occurring after a delay (5 h) was found not to affect memory retention (Graves et al. 2003). These findings reconfirm the time dependency of memory consolidation, emphasizing a critical window for consolidation as demonstrated previously by others (Fishbein et al. 1971; Payne et al. 2012a; Smith 1985, 1995).

7.2 Sleep Deprivation and Glucocorticoid Levels

Sleep deprivation has been linked to variations in responses of the hypothalamic–pituitary–adrenal axis (HPA axis; Meerlo et al. 2008). When the body and brain are under stress, a cycle begins in which the stimulation of corticotropin-releasing hormone (CRH) neurons of the para-ventricular nucleus results in the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH in turn acts on the adrenal cortex, where it stimulates the release of glucocorticoids. States of deprivation have been shown to raise glucocorticoids from normal waking levels (but see Meerlo et al. 2008), but the relationship between glucocorticoid exposure and memory formation tends to follow a bell-shaped curve (see de Kloet et al. 1999; Roozendaal 2000) in both emotional and neutral learning contexts in animals and humans (Cordero and Sandi 1998; Buchanan and Lovallo 2001; Payne et al. 2006, 2007). While increased glucocorticoid levels can lead to memory improvements, particularly when mild to moderate elevations occur during consolidation periods (Roozendaal 2000; Schwabe et al. 2012), extremely or chronically elevated glucocorticoids, as induced by stress from prolonged sleep deprivation, can impair memory (Roozendaal 2000) and have been shown to alter membrane excitability, inhibit synaptic transmission, and cause dendritic atrophy, decreasing the odds of achieving LTP between neurons and inhibiting adult neurogenesis (McDermott et al. 2003, 2006; Davis et al. 2006; Mirescu et al. 2006). Although allowing recovery nights of sleep helps to offset the confounding factor of fatigue in sleep deprivation designs, researchers must nevertheless address the possibility that stress hormones may play a role in the memory impairment produced by sleep deprivation, especially if such deprivation is prolonged or chronic.

7.3 Sleep Deprivation and Connectivity

An important aspect of memory and learning centers on the functional connectivity between different brain areas, facilitating communication between areas, and modulation of one area by another. While sleep deprivation may not always result in behavioral differences between groups, underlying structural compensatory changes may occur. Sleep deprivation may cause the brain to rely on alternative cognitive pathways, which create greater resource demands than would be necessary if sleep had occurred. Orban et al. (2006) examined functional brain activation while subjects completed a spatial memory task during fMRI scanning. As subjects were asked to navigate through a virtual town both at learning and at testing 3 days later, a shift of activation from the hippocampus to a response-based strategy mediated by the striatum was seen in those having had normal sleep on every night, compared to those who were sleep deprived the first night after training. While memory performance did not differ between groups, the caudate nucleus, middle cingulate cortex, precuneus, supplementary parietal lobule, and temporal and frontal cortices were

more active in the non-deprived control group compared to deprived subjects, who still relied heavily on hippocampal networks during task performance.

Clearly, when sleep deprivation follows new learning (and even when it precedes it; Yoo et al. 2007), it impairs memory processing. It is becoming clear that the mechanisms necessary for optimal sleep-dependent memory processing to occur, from the cellular to the network level, are fundamentally compromised by sleep deprivation.

8 Sleep Enhances Emotional Memories

While emotional arousal has been shown to improve memory, resulting in better memory for emotionally salient information, such as negative pictures (Hamann et al. 1999; Kensinger 2009) or words (Kensinger and Corkin 2003), a period of sleep provides additional emotional memory benefits above those seen after wakefulness. Seeing that real emotional events cannot be appropriately manipulated in the laboratory (i.e., witnessing a horrific car accident), researchers have investigated the impact of sleep on memory for artificial emotional and neutral events, including viewing pictures or reading stories. Many studies have utilized the International Affective Picture System (IAPS; Lang et al. 2008), a database including pictures of varying valence and arousal levels, to investigate memory differences for emotional and neutral stimuli. A common practice is to require participants to study a mixture of these pictures prior to a delay that includes either sleep or wakefulness in preparation for a later memory test. As exemplified by Hu et al. (2006), when a full night of sleep occurred during this delay, participants indicated that emotional pictures were more familiar than neutral pictures on a subsequent recognition test, a difference not found for those who maintained daytime wakefulness during the delay. While this study points toward an important function of sleep for emotional memory consolidation, subsequent research has implicated specific sleep stages in the process.

8.1 Implications for REM Sleep in Learning Emotionally Salient Material

Although some recent investigations have discovered a possible role for SWS (Groch et al. 2011), REM sleep is most commonly associated with sleep-dependent preservation of emotional over neutral memories, likely because of the unique neurophysiology associated with this brain state (Sect. 3.3). Consistently, studies have implicated REM duration, proportion of REM with regard to total sleep time, and the electrophysiology of REM in emotional memory performance (Nishida et al. 2009; Payne et al. 2012b). For instance, Nishida et al. (2009) found that taking a 90-min nap after encoding negative and neutral IAPS images resulted in improved memory for emotional pictures that were encoded prior to the nap, compared to a

set encoded after the nap and just 15 min prior to testing. No such improvements were found for those who did not nap. Critically, several characteristics of REM sleep were associated with better memory performance for emotional stimuli, including increased REM amount, reduced REM latency, and intensified theta rhythms occurring during this stage. These findings extend previous work using these stimuli (Hu et al. 2006) by indicating a role for qualities of REM sleep in successful memory processing for emotionally salient information.

REM sleep has been implicated not only in the preservation of memory for emotional materials in their entirety, but also the selective consolidation of only those portions of learned materials that are most emotional. One study manipulated pictures so that they consisted of either a negative or neutral foreground object placed on a neutral background (Payne et al. 2008). After participants had encoded the intact scenes, they underwent a period of nocturnal sleep or daytime wakefulness before a surprise recognition test of the separated scene objects and backgrounds. Results revealed an emotional memory trade-off, whereby memory for the negative foreground objects was improved relative to the neutral objects, while memory for the backgrounds paired with the negative objects was reduced compared to the backgrounds paired with neutral objects. Importantly, they found that this trade-off was augmented after a period of sleep, with memory for negative objects improved above that seen after waking, as well as after just a 30-min delay. Similar to previous research (Nishida et al. 2009), this preferential enhancement for negative object memory after sleep is associated with increased amounts of REM sleep achieved during the night (Payne et al. 2012b).

Such selective memory enhancements for emotional information have also been suggested to arise from neural reorganization specific to a period of sleep. Compared to wakefulness, the successful retrieval of negative objects in the emotional memory trade-off task not only employed a more efficient brain network after sleep, with activations restricted to the amygdala, ventromedial PFC, and cingulate gyrus, but also increased connectivity between the amygdala, hippocampus, and ventromedial PFC (Payne and Kensinger 2011). As discussed in Sect. 2, the amygdala is important for emotional learning through its modulation of the memory centers of the brain (McGaugh 2004), to which it is closely interconnected (Ritchey et al. 2008). However, the amygdala is also strongly connected to the ventromedial prefrontal cortex (vmPFC), which has been shown to exert top-down control over the processing of emotional information within the amygdala (Sotres-Bayon et al. 2004). Thus, sleep appears to target brain circuitry vital for proper emotional memory formation, making interactions between these areas more effective just 12 h post-learning.

8.2 Long-Term Effects of Sleep on Emotional Memory

Sleeping during the first post-encoding night not only protects memory for emotional information the following day, but also results in lasting memory benefits seen up to years later. Using emotional and neutral narratives, Wagner et al. (2001)

found that memory for emotional texts was better preserved than neutral ones immediately following post-learning sleep occurring during the second half of the night (rich in REM sleep), rather than during the first half of the night (rich in SWS). However, upon testing these subjects 4 years later, they found that while sleep continued to enhance memory for emotional relative to neutral descriptions more so than wake, both early- and late-sleep groups performed equally well. Although this may seem counterintuitive, the authors explain that those in the early-sleep group, who initially performed more poorly than the late-sleep group, went back to sleep following the first test, eventually receiving the second REM-rich half of the night. Thus, selective consolidation processes active during REM may have still been available to this group, allowing them to adequately process the stimuli for the follow-up test.

In addition to memory performance, changes seen at the neural level immediately after sleep also continue to develop long after the learning event. Three days after learning, retrieving emotional IAPS pictures was shown to recruit the hippocampus and medial PFC to a greater extent in those who slept after initial learning as opposed to those who were sleep deprived (Sterpenich et al. 2007). Such evidence is consistent with brain imaging results obtained during memory retrieval of emotional materials after only a 12-h delay (Payne and Kensinger 2011) and suggests that this brain circuitry is engaged in emotional processing from hours to days following the initial post-learning sleep episode. However, when participants were re-tested after a delay of 6 months, the activation pattern shifted to a network including the amygdala, frontal cortical areas such as the ventromedial PFC, and the middle occipital cortex (Sterpenich et al. 2009). Such a transition, seen only in the group that slept after learning, again highlights the importance of sleeping soon after learning to promote long-term neural changes that influence emotional processing and benefit memory.

9 The Effect of Sleep on Emotional Reactivity and Regulation

Clearly, the effect of sleep on emotional memorysleep and neural processing of emotional stimuli is well documented. However, the picture of how sleep affects subjective and visceral reactivity to emotional stimuli remains unclear, in spite of aphorisms such as “Sleep on it; things will look brighter in the morning!”

Previous research shows that negative stimuli, in addition to being subjectively rated as more emotionally salient at encoding, also create greater changes in physiology, such as heart rate, skin conductance response (SCR; Lang et al. 1993), amygdala activation (Garavan et al. 2001), and event-related potentials (ERP; Schupp et al. 2006; Diedrich et al. 1997) when compared to their neutral counterparts. Recently, a controversy has arisen in the literature as to whether a night of sleep potentiates or depotentiates autonomic reactivity to these negative stimuli.

9.1 The Potentiating or Stabilizing Effect of Sleep on Reactivity

In an early attempt to address this question, Wagner et al. (2002) assessed affective responses after assigning participants into groups receiving either early SWS-rich or late REM-rich periods of overnight sleep. Those that rated affectivity after 3 h of REM-rich sleep ascribed a significant increase in aversiveness to negative scenes, while those receiving 3 h of early SWS-rich sleep did not have a significant shift in reported reactivity from baseline ratings. An additional experiment found that after a total night of sleep, there was also a shift toward increased aversiveness, comparable to that seen after the late-night REM-rich sleep (Wagner et al. 2002). Baran et al. (2012) reported similar findings in a study examining both emotional memory as well as changes in subjective emotional reactivity after delays that included sleep or wake. Results indicated a boost in memory for negatively salient scenes, as expected, but rather than finding an increase in subjective negativity after a night of sleep, they found that the negative emotional response was preserved over a night of sleep when compared to a clear attenuation of negative ratings seen in the wake group (Baran et al. 2012).

Additional research was conducted examining both behavioral and electrophysiological measures during periods of late REM-rich and early SWS-rich retention sleep. Groch et al. (2012) discovered that memory for emotionally salient stimuli was significantly enhanced during a consolidation period containing REM-rich sleep compared to a period of SWS-rich sleep. Additionally, they found that while there was no difference in ratings pre- or post-sleep in either condition, REM-rich sleep correlated with increased ERP positivity over the frontal cortex 300–500 ms after stimulus onset when presented with "old" negative pictures compared to "new" negative pictures at recognition (Groch et al. 2012). Such an increase, not seen after SWS-rich sleep, has been associated with increased memory for an item (Woroch and Gonsalves 2010). Concurrently, ERP reactivity during recognition of familiar negative scenes 500–800 ms post-stimulus, a period linked to emotionality of the stimuli, remained unchanged after both REM- and SWS-rich sleep. From this, Groch et al. concluded that REM sleep benefits memory for emotional content without a change in emotional reactivity (Groch et al. 2012).

9.2 The Depotentiating Effect of Sleep on Reactivity

In contrast to the studies just discussed, several studies report a *reduction* in reactivity to emotional stimuli after a period of sleep, particularly REM sleep. One 1972 study by Greenberg et al. separated participants into REM deprivation (REMD), NREM interruptions (NREM-I), and normal sleep groups. They found that participants in the REMD condition habituated less to gruesome footage of an autopsy than either of the other groups and concluded that REM sleep must be

important for adaptation to a previously experienced anxiety-provoking situation. A more recent fMRI study replicated these findings (Rosales-Lagarde et al. 2012). Participants experienced REMD or NREM-I between the completion of two emotional reactivity tasks separated by a 24-h delay. Participants in the NREM-I condition demonstrated a decrease in behavioral emotional reactivity compared to the REMD group and numerous neural networks associated with emotional processing showed a reduction in activation, including the ventrolateral prefrontal cortex, indicating reduced need for top-down emotion regulation. Activation in the same areas after REMD remained the same or increased, indicating that deprivation of REM sleep impairs our ability to regulate our emotional responsiveness.

Another recent study investigated how a daytime nap would affect reactivity to emotional faces (Gujar et al. 2011). Participants were separated into nap and no-nap conditions after viewing affective faces early in the afternoon. Those who were allowed to nap had reduced ratings of fearful expressions while their ratings of happy facial expressions increased. Those who remained awake during the delay showed an increase in ratings of fear and anger expressions. A study by Pace-Schott et al. (2011) also utilized a napping paradigm. They found that after repeated intra-session viewing of negative scenes, a nap resulted in greater SCR and corrugator electromyogram (EMG) habituation to previously encountered negative stimuli compared to a wake group, without a change in subjective ratings (Pace-Schott et al. 2011).

Importantly, studies utilizing undisturbed nights of sleep have also suggested that sleep plays an important role in depotentiating reactivity. For instance, Cunningham et al. (In Press) collected SCR and HRD measures during encoding and recognition sessions of negative and neutral stimuli. Participants were dismissed for a 12-h consolidation period of daytime wakefulness or nocturnal sleep between sessions. Those who slept showed a significant decrease in SCR and HRD activation to all stimuli from encoding to recognition, while reactivity to the stimuli for those who stayed awake remained unchanged. Van der Helm et al. (2011) used fMRI to find that amygdala reactivity was attenuated in response to previously viewed negative stimuli after a night of sleep. This decrease in amygdala activation was partnered with an increase in ventromedial prefrontal cortex (vmPFC) connectivity. As discussed. the vmPFC has been indicated in top-down inhibitory effects on amygdala activation for healthy, rested adults (Sotres-Bayon et al. 2004). This change in neural reactivity was accompanied by a decrease in subjective emotional reactivity to negative scenes previously encountered (van der Helm et al. 2011). These results have given increased credibility to the REM sleep hypothesis of emotional memory processing (van der Helm and Walker 2009; Walker 2009), portrayed graphically in Fig. 8. According to this theory, at encoding, an emotional memory is comprised of a memory and a significant affective tone. After a single night of sleep, the affective tone is partially reduced, and subsequent nights of sleep continue to chip away at the emotional salience until only the memory remains.

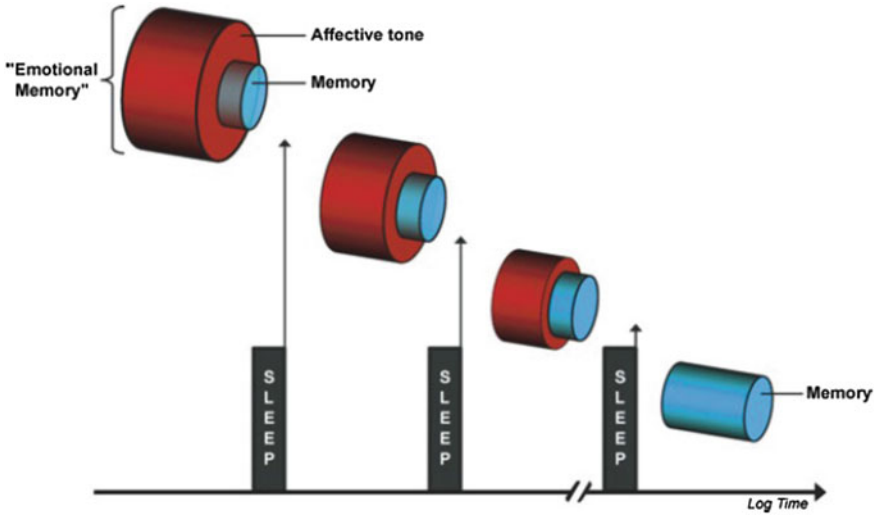

Fig. 8 A visual representation of the REM sleep hypothesis of emotion regulation. When an emotional experience is first encoded, it is wrapped in a very strong affective tone that initially helps consolidate the memory. After subsequent nights of sleep including REM, the emotional charge is stripped away until only the memory remains (Walker 2009)

10 Future Directions

As research methods and techniques continue to grow more sophisticated, our ability to investigate the mysteries of declarative memory has become more refined. As we have extensively detailed throughout this chapter, the understanding of the role that sleep plays in the consolidation of these types of memories has surged over the last several decades. Despite this blitz of information, many questions remain unanswered. For example, the common comparison of overnight sleep to daytime naps begs the question of whether daytime and nocturnal sleep periods that are differentiated by varying neurochemical milieus and potentially distinct sleep stage compositions actually represent equivalent processes or perhaps contribute differently to memory consolidation. Further exploration should also be directed toward the impact of sleep on the consolidation of autobiographical memories, and whether active sleep processes and synaptic homeostasis work together or independently to strengthen memories.

As Sect. 9 depicts, our understanding of how sleep may modulate emotional affectivity is still equivocal. While one line of evidence suggests the enhancement or preservation of emotional salience of negative scenes by REM sleep, the other asserts that it has an attenuating role. As we continue to learn more about this relationship, the role of sleep in psychophysiology may have far-reaching clinical implications as well. Sleep disturbance could be a core component in certain psychopathologies marked with a struggle to separate emotional salience from

memory, such as mood and anxiety disorders (particularly PTSD). Further exploration into the function of sleep could be vital not only to our understanding of the underlying mechanisms of this disorder, but also in our ability to develop potential treatments.

Finally, there is still much to be learned by probing deeper into the electrophysiological phenomena that occur during sleep, in an attempt to gain greater understanding of the active role for sleep in memory processing beyond simple sleep stage correlations. While research has focused on the separation of sleep into different stages, allowing us to gain a better understanding of the contributions of these components to memory and emotional processing, sleep itself may be more than the sum of its parts. Future research should not only continue to refine our knowledge of sleep stages individually but also should integrate across these findings to create a better understanding of sleep as a whole.

11 Conclusion

Mounting evidence suggests that sleep contributes to the active processing of recently acquired information. It does so through a host of neurochemical and electrophysiological mechanisms that vary across the different sleep stages to create the ideal opportunity for memory consolidation. Both nocturnal and daytime sleep episodes of varying lengths have been shown to benefit declarative memory processing, particularly when sleep closely follows the learning event. Beyond simply preserving memories, sleep also promotes the flexible recombination of information, resulting in gist extraction and insight, as well as the selective preservation of emotionally salient information over neutral information. This chapter highlights the contemporary knowledge of how sleep affects the consolidation of emotional memory in humans; however, a great deal of questions remains and new research continues to provide breakthroughs in our understanding. While much light has been shed on the crucial cognitive functions of sleep, the impact of sleep on memory processing remains a fruitful area for future research.

References

Alger SE, Lau H, Fishbein W (2010) Delayed onset of a daytime nap facilitates retention of declarative memory. PLoS ONE 5(8):e12131. doi:10.1371/journal.pone.0012131

Alger SE, Lau H, Fishbein W (2012) Slow wave sleep during a daytime nap is necessary for protection from subsequent interference and long-term retention. Neurobiol Learn Mem 98:188-196. http://dx.doi.org/10.1016/j.nlm.2012.06.003

Aston-Jones G (2004) The locus coeruleus, A5 and A7 noradrenergic cell groups. In: Paxinos G (ed) The rat nervous system. Elsevier Academic Press, San Diego, pp 259–294

Backhaus J, Hoeckesfeld R, Born J, Hohagen F, Junghanns K (2007) Immediate as well as delayed post learning sleep but not wake enhances declarative memory consolidation in children. Neurobiol Learn Mem 89:76–80

Baran B, Pace-Schott EF, Ericson C, Spencer RM (2012) Processing of emotional reactivity and emotional memory over sleep. J Neurosci 32(3):1035–1042

Battaglia FP, Sutherland GR, McNaughton BL (2004) Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. Learn Mem 11(6):697–704

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356

Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P et al (1997) Regional cerebral blood flow throughout the sleep-wake cycle. An H2 (15) O PET study. Brain 120 (7):1173–1197

Brehens CJ, van den Boom LP, de Hoz L, Friedman A, Heinemann U (2005) Induction of sharp-wave ripple complexes in vitro and reorganization of hippocampal networks. Nat Neurosci 8 (11):1560–1567

Buchanan TW, Lovallo WR (2001) Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 26(3):307–317

Buzsaki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31:551–570

Buzsaki G, Leung LW, Vanderwolf CH (1983) Cellular bases of hippocampal EEG in the behaving rat. Brain Res 287(2):139–171

Buzsaki G, Csicsvari J, Dragoi G, Harris K, Henze D, Hirase H (2002) Homeostatic maintenance of neuronal excitability by burst discharges in vivo. Cereb Cortex 12:893–899

Carskadon MA, Dement WC (1989) Normal human sleep: an overview. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W.B. Saunders, Philadelphia, pp 3–13

Chen C, Hardy M, Zhang J, LaHoste GJ, Bazan NG (2006) Altered NMDA receptor trafficking contributes to sleep deprivation-induced hippocampal synaptic and cognitive impairments. Biochem Biophys Res Commun 340:435–440

Chrobak JJ, Buzsaki G (1994) Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. J Neurosci 14:6160–6170

Clemens Z, Fabo D, Halasz P (2005) Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience 132:529–535

Cordero MI, Sandi C (1998) A role for brain glucocorticoid receptors in contextual fear conditioning: dependence upon training intensity. Brain Res 786:11–17

Cunningham TJ, Crowell CR, Alger SE, Kensinger EA, Villano M, Mattingly SM, Payne JD (In Press) Psychophysiological arousal at encoding leads to reduced reactivity but enhanced emotional memory after sleep. Neurobiology of Learning and Memory

Davis CJ, Meighan PC, Taishi P, Krueger JM, Harding JW, Wright JW (2006) REM sleep deprivation attenuates actin-binding protein cortactin: a link between sleep and hippocampal plasticity. Neurosci Lett 400:191–196

De Gennaro L, Ferrara M (2003) Sleep spindles: an overview. Sleep Med Rev 7(5):423–440

Deboer, T (2013) Behavioral and electrophysiological correlates of sleep and sleep homeostasis. Springer, Heidelberg

de Kloet ER, Oitzl MS, Joëls M (1999) Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci 22(10):422–426

Diba K, Buzsaki G (2007) Forward and reverse hippocampal place-cell sequences during ripples. Nat Neurosci 10(10):1241–1242

Diedrich O, Naumann E, Maier S, Becker G (1997) A frontal positive slow wave in the ERP associated with emotional slides. J Psychophysiol

Diekelmann S, Landolt HP, Lahl O, Born J, Wagner U (2008) Sleep loss produces false memories. PLoS ONE 3(10):e3512

Durrant SJ, Taylor C, Cairney S, Lewis PA (2011) Sleep-dependent consolidation of statistical learning. Neuropsychologia 49(5):1322–1331

Ego-Stengel V, Wilson MA (2010) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20:1–10

Ellenbogen JM, Payne JD, Stickgold R (2006) The role of sleep in declarative memory consolidation: passive, permissive, active or none? Curr Opin Neurobiol 16:716–722
Ellenbogen JM, Hu PT, Payne JD, Titone D, Walker MP (2007) Human relational memory requires time and sleep. Proc Natl Acad Sci USA 104(18):7723–7728
Eschenko O, Mölle M, Born J, Sara SJ (2006) Elevated sleep spindle density after learning or after retrieval in rats. J Neurosci 26(50):12914–12920
Eschenko O, Sara SJ (2008) Learning-dependent, transient increase of activity in noradrenergic neurons of locus coeruleus during slow wave sleep in the rat: brain stem-cortex interplay for memory consolidation? Cereb Cortex 18(11):2596–2603
Eschenko O, Ramadan W, Mölle M, Born J, Sara SJ (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 15(4):222–228
Fenn KM, Nusbaum HC, Margoliash D (2003) Consolidation during sleep of perceptual learning of spoken language. Nature 425(9):614–616
Ferrara M, Iaria G, De Gennaro L, Guariglia C, Curcio G, Tempesta D, Bertini M (2006) The role of sleep in the consolidation of route learning in humans: a behavioural study. Brain Res Bull 71:4–9
Fischer S, Drosopoulos S, Tsen J, Born J (2006) Implicit learning–explicit knowing: a role for sleep in memory system interaction. J Cogn Neurosci 18(3):311–319
Fishbein W, McGaugh JL, Swarz JR (1971) Retrograde amnesia: electroconvulsive shock effects after termination of rapid eye movement sleep deprivation. Science 172:80–82
Gais S, Mölle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22(15):6830–6834
Gais S, Born J (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc Natl Acad Sci USA 101(7):2140–2144
Gais S, Lucas B, Born J (2006) Sleep after learning aids memory recall. Learn Mem 13:259–262
Gais S, Rasch B, Dahmen JC, Sara S, Born J (2011) The memory function of noradrenergic activity in non-REM sleep. J Cogn Neurosci 23(9):2582–2592
Garavan H, Pendergrass JC, Ross TJ, Stein EA, Risinger RC (2001) Amygdala response to both positively and negatively valenced stimuli. NeuroReport 12(12):2779–2783
Graves LA, Heller EA, Pack AI, Abel T (2003) Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. Learn Mem 10:168–176
Girardeau G, Benchenane K, Wiener SI, Buzsaki G, Zugaro MB (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12:1222–1223
Greenberg R, Pillard R, Pearlman C (1972) The effect of dream (stage REM) deprivation on adaptation to stress. Psychosom Med 34(3):257–262
Groch S, Wilhelm I, Diekelmann S, Sayk F, Gais S, Born J (2011) Contribution of norepinephrine to emotional memory consolidation during sleep. Psychoneuroendocrinology 36(9):1342–1350
Groch S, Wilhelm I, Diekelmann S, Born J (2012) The role of REM sleep in the processing of emotional memories: Evidence from behavior and event-related potentials. Neurobiol Learn Mem
Gujar N, McDonald SA, Nishida M, Walker MP (2011) A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. Cereb Cortex 21(1):115–123
Hamann S (2001) Cognitive and neural mechanisms of emotional memory. Trends Cogn Sci 5 (9):394–400
Hamann SB, Ely TD, Grafton ST, Kilts CD (1999) Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci 2(3):289–293
Hamann SB, Ely TD, Hoffman JM, Kilts CD (2002) Ecstasy and agony: activation of human amygdala in positive and negative emotion. Psychol Sci 13(2):135–141
Hasselmo ME (1999) Neuromodulation: acetylcholine and memory consolidation. Trends Cogn Sci 3(9):351–359
Hasselmo ME, Bower JM (1992) Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex. J Neurophysiol 67:1222–1229

Hasselmo ME, McGaughy J (2004) High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. Prog Brain Res 145:207–231
Hebb DO (1949) The organization of behavior. Wiley, New York
Heine R (1914) Über Wiedererkennen und Rückwirkende Hemmung. Zeitschrift für Psychologie mit Zeitschrift für angewandte Psychologie 68:161–236
Hennevin E, Huetz C, Edeline JM (2007) Neural representations during sleep: from sensory processing to memory traces. Neurobiol Learn Mem 87(3):416–440
Herreras O, Solis JM, Munoz MD, Martin del Rio R, Lerma J (1988) Sensory modulation of hippocampal transmission: I. Opposite effects on CA1 and dentate gyrus synapsis. Brain Res 461:290–302
Hoffman KL, McNaughton BL (2002) Coordinated reactivation of distributed memory traces in primate neocortex. Science 297(5589):2070–2073
Hounsgaard J (1978) Presynaptic inhibitory action of acetylcholine in area CA1 of the hippocampus. Exp Neurol 62:787–797
Hu P, Stylos-Allan M, Walker MP (2006) Sleep facilitates consolidation of emotional declarative memory. Psychol Sci 17(10):891–898
Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78–81
Iber C, Ancoli-Israel S, Chesson AL, Quan SF (eds) (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications, 1st edn. American Academy of Sleep Medicine, Westchester
Jenkins JG, Dallenbach KM (1924) Obliviscence during sleep and waking. Am J Psychol 35:605–612
Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10(1):100–107
Karacan I, Williams RL, Finley WW, Hursch CJ (1970) The effects of naps on nocturnal sleep: influence on the need for Stage-1 REM and Stage 4 sleep. Biol Psychiatry
Kensinger EA (2009) What factors need to be considered to understand emotional memories? Emot Rev 1(2):120–121
Kensinger EA, Corkin S (2003) Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words? Mem Cogn 31(8):1169–1180
Kensinger EA, Schacter DL (2006) Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. J Neurosci 26 (9):2564–2570
Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19:4090–4101
Lahl O, Wispel C, Willigens B, Pietrowsky R (2008) An ultra short episode of sleep is sufficient to promote declarative memory performance. J Sleep Res 17:3–10
Lang A, Dhillon K, Dong Q (1995) The effects of emotional arousal and valence on television viewers' cognitive capacity and memory. J Broadcast Electron Media 39(3):313–327
Lang P, Greenwald MK, Bradley M, Hamm A (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30(3):261–273
Lang PJ, Bradley MM, Cuthbert BN (2008) International affective picture system (IAPS): affective ratings of pictures and instruction manual, technical report A-8. University of Florida, Gainesville
Lau H, Tucker MA, Fishbein W (2010) Daytime napping: effects on human direct associative and relational memory. Neurobiol Learn Mem 93(4):554–560
Lau H, Alger SE, Fishbein W (2011) Relational memory: a daytime nap facilitates the abstraction of general concepts. PLoS ONE 6(11):e27139. doi:10.1371/journal.pone.0027139
LeDoux J (2002) Synaptic self: how our brains become who we are. Penguin Putnam Inc, New York
Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29(1):145–156

Maquet P, Péters JM, Aerts J, Delfiore G, Degueldre C, Luxen A, Franck G (1996) Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383(6596):163–166
Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C et al (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3:831–836
Marshall L, Molle M, Hallschmid M, Born J (2004) Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 24(44):9985–9992
Marshall L, Helgadottir H, Molle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613
McClelland JL, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol Rev 102(3):419–457
McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003) Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 22(29):9687–9695
McDermott CM, Hardy MN, Bazan NG, Magee JC (2006) Sleep deprivation- induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. J Physiol 570 (3):553–565
McGaugh JL (2000) Memory—a century of consolidation. Science 287:248–251
McGaugh JL (2004) The amygdala modulates the consolidation of memories of emotionally arousing experiences. Ann Rev Neurosci 27:1–28
Meerlo P, Sgoifo A, Suchecki D (2008) Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev 12(3):197–210
Mirescu C, Peters JD, Noiman L, Gould E (2006) Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glucocorticoids. PNAS 103(50):19170–19175
Mölle M, Yeshenko O, Marshall L, Sara SJ, Born J (2006) Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. J Neurophysiol 96(1):62–70
Mölle M, Eschenko O, Gais S, Sara SJ, Born J (2009) The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci 29 (5):1071–1081
Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C et al (2005) Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 207(1):35–66
Nadasdy Z, Hirase H, Czurko A, Csicsvari J, Buzsaki G (1999) Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 19:9497–9507
Nishida M, Pearsall J, Buckner RL, Walker MP (2009) REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 19:1158–1166
Ochsner KN (2000) Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. J Exp Psychol Gen 129(2):242–261
O'Neill J, Pleydell-Bouverie B, Dupret D, Csicsvari J (2010) Play it again: reactivation of waking experience and memory. Trends Neurosci 33(5):220–229
Orban P, Rauchs G, Balteau E, Degueldre C, Luxen A, Maquet P, Peigneux P (2006) Sleep after spatial learning promotes covert reorganization of brain activity. PNAS 103(18):7124–7129
Pace-Schott EF, Shepherd E, Spencer R, Marcello M, Tucker M, Propper RE, Stickgold R (2011) Napping promotes inter-session habituation to emotional stimuli. Neurobiol Learn Mem 95 (1):24–36
Pavlides C, Winson J (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. J Neurosci 9:2907–2918
Payne JD (2011) Learning, memory, and sleep in humans. Sleep Med Clin 6(1):15–30
Payne JD, Kensinger EA (2010) Sleep's role in the consolidation of emotional episodic memories. Curr Dir Psychol Sci 19(5):290–295
Payne JD, Kensinger EA (2011) Sleep leads to changes in the emotional memory trace: evidence from fMRI. J Cogn Neurosci 23(6):1285–1297

Payne JD, Nadel L, Britton WB, Jacobs WJ (2004) The biopsychology of trauma and memory. In: Reisberg D, Hertel P (eds) Memory and emotion. Oxford University Press, New York, pp 76–128

Payne JD, Jackson ED, Ryan L, Hoscheidt S, Jacobs WJ, Nadel L (2006) The impact of stress on memory for neutral vs. emotional aspects of episodic memory. Mem 14:1–16

Payne JD, Jackson ED, Hoscheidt S, Ryan L, Jacobs WJ, Nadel L (2007) Stress administered prior to encoding impairs neutral but enhances emotional long-term episodic memories. Learn Mem 14:861–868

Payne JD, Stickgold R, Swanberg K, Kensinger EA (2008) Sleep preferentially enhances memory for emotional components of scenes. Psychol Sci 19:781–788

Payne JD, Schacter DL, Propper RE, Huang LW, Wamsley EJ, Tucker MA, Stickgold R (2009) The role of sleep in false memory formation. Neurobiol Learn Mem 92(3):327–334

Payne JD, Tucker MA, Ellenbogen JM, Wamsley EJ, Walker MP, Schacter DL, Stickgold R (2012a) Memory for semantically related and unrelated declarative information: the benefit of sleep, the cost of wake. PLoS ONE 7(3):e33079

Payne JD, Chambers AM, Kensinger EA (2012b) Sleep promotes lasting changes in selective memory for emotional scenes. Front Integr Neurosci 6

Peigneux P, Laureys S, Delbeuck X, Maquet P (2001) Sleeping brain, learning brain. the role of sleep for memory systems. NeuroReport 12:111–124

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Foire G, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow-wave sleep? Neuron 44:535–545

Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9:534–547

Plihal W, Born J (1999a) Memory consolidation in human sleep depends on inhibition of glucocorticoid release. NeuroReport 10:2741–2747

Plihal W, Born J (1999b) Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 36(5):571–582

Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW (1997) Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science 276 (5316):1265–1268

Ramadan W, Eschenko O, Sara SJ (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. PLoS ONE 4(8):e6697

Rasch B, Büchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315(5817):1426–1429

Rechtschaffen A, Kales A (eds) (1968) A manual of standardized terminology, techniques and scoring system for sleep stages in human subjects. Brain Information Service/Brain Research Institute, University of California, Los Angeles

Retey JV, Adam M, Honegger E, Khatami R, Luhmann UFO et al (2005) A functional genetic variation of adenosine affects the duration and intensity of deep sleep in humans. PNAS 102 (43):15676–15681

Ritchey M, Dolcos F, Cabeza R (2008) Role of amygdala connectivity in the persistence of emotional memories over time: an event related fMRI investigation. Cereb Cortex 18(11):2494–2504

Roediger HL, McDermott KB (1995) Creating false memories: remembering words not presented in lists. J Exp Psychol Learn Mem Cogn 21(4):803

Roozendaal B (2000) Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology 25:213–238

Rosanova M, Ulrich D (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25(41):9398–9405

Rosales-Lagarde A, Armony JL, del Río-Portilla Y, Trejo-Martínez D, Conde R, Corsi-Cabrera M (2012) Enhanced emotional reactivity after selective REM sleep deprivation in humans: an fMRI study. Front Behav Neurosci 6(25):1–13

Rovira C, Ben-Ari Y, Cherubini E, Krnjevic K, Ropert N (1983) Pharmacology of the dendritic action of acetylcholine and further observations on the somatic disinhibition in the rat hippocampus in situ. Neuroscience 8:97–106

Saletin JM, Goldstein AN, Walker MP (2011) The role of sleep in directed forgetting and remembering of human memories. Cereb Cortex 21(11):2534–2541

Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 10(3):211–223

Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P, Klimesch W, Saletu B, Zeitlhofer J (2004) Sleep spindles and their significance for declarative memory consolidation. Sleep 27(8):1479–1485

Schabus M, Hodlmoser K, Pecherstorfer T, Klosch G (2005) Influence of midday naps on declarative memory performance and motivation. Somnologie 9(3):148–153

Schmidt C, Peigneux P, Muto V, Schenkel M, Knoblauch V, Münch M et al (2006) Encoding difficulty promotes post learning changes in sleep spindle activity during napping. J Neurosci 26(35):8976–8982

Schoen LS, Badia P (1984) Facilitated recall following REM and NREM naps. Psychophysiology 21(3):299–306

Schupp HT, Flaisch T, Stockburger J, Junghofer M (2006) Emotion and attention: event-related brain potential studies. Prog Brain Res 156:31

Schwabe L, Joels M, Roozendaal B, Wolf OT, Oitzl MS (2012) Stress effects on memory: an update and integration. Neurosci Biobehav Rev 36:1740–1749

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21

Sharot T, Yonelinas AP (2008) Differential time-dependent effects of emotion on recollective experience and memory for contextual information. Cognition 106(1):538–547

Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21:1123–1128

Sirota A, Csicsvari J, Buhl D, Buzsáki G (2003) Communication between neocortex and hippocampus during sleep in rodents. Proc Natl Acad Sci USA 100(4):2065–2069

Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271:1870–1873

Smith CT (1985) Sleep states and learning: a review of the animal literature. Neurosci Biobehav Rev 9(2):157–168

Smith CT (1995) Sleep states and memory processes. Behav Brain Res 69(1–2):137–145

Smith CT, Aubrey JB, Peters KR (2004) Different roles for REM and stage 2 sleep in motor learning: a proposed model. Psychologica Belgica 44(1–2):81–104

Sotres-Bayon F, Bush DE, LeDoux JE (2004) Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn Mem 11(5):525–535

Steriade M, Timofeev I (2003) Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 37(4):563–576

Steriade M, Nuñez A, Amzica F (1993) Intracellular analysis of relations between the slow (< 1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci 13(8):3266–3283

Sterman MB, Goodman SJ, Kovalesky RA (1978) Effects of sensorimotor EEG feedback training on seizure susceptibility in the rhesus monkey. Exp Neurol 62(3):735–747

Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A et al (2007) Sleep- related hippocampal-cortical interplay during emotional memory recollection. PLoS ONE 5(11):e282

Sterpenich V, Albouy G, Darsaud A, Schmidt C, Vandewalle G et al (2009) Sleep promotes the neural reorganization of remote emotional memories. J Neurosci 29(16):5143–5152

Stickgold R, Ellenbogen JM (2008) Quiet! Sleeping brain at work. Sci Am Mind 19(4):22–29

Stickgold R, Hobson JA, Fosse R, Fosse M (2001) Sleep, learning, and dreams: off-line memory reprocessing. Science 294:1052–1057

Stickgold R, Walker M (2004) To sleep, perchance to gain creative insight? Trends Cogn Sci 8 (5):191–192

Stickgold R, Walker MP (2013) Sleep-dependent memory triage: evolving generalization through selective processing. Nat Neurosci 16(2):139–145
Sweatt JD (1999) Toward a molecular explanation for long-term potentiation. Learn Mem 6:399–416
Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernández G (2006) Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci USA 103(3):756–761
Talamini LM, Nieuwenhuis IL, Takashima A, Jensen O (2008) Sleep directly following learning benefits consolidation of spatial associative memory. Learn Mem 15(4):233–237
Tamminen J, Payne JD, Stickgold R, Wamsley EJ, Gaskell MG (2010) Sleep spindle activity is associated with the integration of new memories and existing knowledge. J Neurosci 30 (43):14356–14360
Tanguay PE, Ornitz EM, Kaplan A, Bozzo ES (1975) Evolution of sleep spindles in childhood. Electroencephalogr Clin Neurophysiol 38(2):175–181
Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
Tucker MA, Fishbein W (2008) Enhancement of declarative memory performance following a daytime nap is contingent on strength of initial task acquisition. Sleep 31(2):197–203
Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W (2006) A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem 86(2):241–247
Tulving E (1985) Memory and consciousness. Can Psychol 26:1–12
Valentino RJ, Dingledine R (1981) Presynaptic inhibitory effect of acetylcholine in the hippocampus. J Neurosci 1:784–792
van Der Helm E, Walker MP (2009) Overnight therapy? The role of sleep in emotional brain processing. Psychol Bull 135(5):731
van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP (2011) REM sleep depotentiates amygdala activity to previous emotional experiences. Curr Biol
Van Der Werf YD, Altena E, Schoonheim MM, Sanz-Arigita EJ, Vis JC, De Rijke W, Van Someren EJ (2009) Sleep benefits subsequent hippocampal functioning. Nat Neurosci 12:122–123
Vazquez J, Baghdoyan HA (2001) Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. Am J Physiol Regul Integr Comp Physiol 280(2): R598–R601
Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, … Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. Nature 461(7267):1122–1125
Vertes RP, Siegel JM (2005) Time for the sleep community to take a critical look at the purported role of sleep in memory processing. Sleep 28(10):1228–1229 (discussion 1230–1233)
Wagner U, Gais S, Born J (2001) Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem 8:112–119
Wagner U, Fischer S, Born J (2002) Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. Psychosom Med 64 (4):627–634
Wagner U, Gais S, Haider H, Verleger R, Born J (2004) Sleep inspires insight. Nature 427 (6972):352–355
Walker MP (2009) The role of sleep in cognition and emotion. Ann New York Acad Sci 1156 (1):168–197
Walker MP, Stickgold R (2006) Sleep, memory, and plasticity. Annu Rev Psychol 57:139–166
Wamsley EJ, Tucker MA, Payne JD, Stickgold R (2010) A brief nap is beneficial for human route-learning: the role of navigation experience and EEG spectral power. Learn Mem 17 (7):332–336
Webb WB, Agnew HW, Sternthall H (1966) Sleep during the early morning. Psychonom Sci 6:277–278
Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006) Learning induces long- term potentiation in the hippocampus. Science 313:1093–1097

Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265(5172):676–679

Wixted JT (2004) The psychology and neuroscience of forgetting. Ann Rev Psychol 55:235–269

Woroch B, Gonsalves BD (2010) Event-related potential correlates of item and source memory strength. Brain Res 1317:180–191

Yang RH, Hu SJ, Wang Y, Zhang WB, Luo WJ, Chen JY (2008) Paradoxical sleep deprivation impairs spatial learning and affects membrane excitability and mitochondrial protein in the hippocampus. Brain Res 1230:224–232

Yoo S, Hu PT, Gujar N, Jolesz FA, Walker M (2007) A deficit in the ability to form new human memories without sleep. Nat Neurosci 10:385–392

Zeitlhofer J, Gruber G, Anderer P, Asenbaum S, Schimicek P, Saletu B (2003) Topographic distribution of sleep spindles in young healthy subjects. J Sleep Res 6(3):149–155

Sleep-Dependent Memory Consolidation in Healthy Aging and Mild Cognitive Impairment

Edward F. Pace-Schott and Rebecca M. C. Spencer

Abstract Sleep quality and architecture as well as sleep's homeostatic and circadian controls change with healthy aging. Changes include reductions in slow-wave sleep's (SWS) percent and spectral power in the sleep electroencephalogram (EEG), number and amplitude of sleep spindles, rapid eye movement (REM) density and the amplitude of circadian rhythms, as well as a phase advance (moved earlier in time) of the brain's circadian clock. With mild cognitive impairment (MCI) there are further reductions of sleep quality, SWS, spindles, and percent REM, all of which further diminish, along with a profound disruption of circadian rhythmicity, with the conversion to Alzheimer's disease (AD). Sleep disorders may represent risk factors for dementias (e.g., REM Behavior Disorder presages Parkinson's disease) and sleep disorders are themselves extremely prevalent in neurodegenerative diseases. Working memory, formation of new episodic memories, and processing speed all decline with healthy aging whereas semantic, recognition, and emotional declarative memory are spared. In MCI, episodic and working memory further decline along with declines in semantic memory. In young adults, sleep-dependent memory consolidation (SDC) is widely observed for both declarative and procedural memory tasks. However, with healthy aging, although SDC for declarative memory is preserved, certain procedural tasks, such as motor-sequence learning, do not show SDC. In younger adults, fragmentation of sleep can reduce SDC, and a normative

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increase in sleep fragmentation may account for reduced SDC with healthy aging. Whereas sleep disorders such as insomnia, obstructive sleep apnea, and narcolepsy can impair SDC in the absence of neurodegenerative changes, the incidence of sleep disorders increases both with normal aging and, further, with neurodegenerative disease. Specific features of sleep architecture, such as sleep spindles and SWS are strongly linked to SDC. Diminution of these features with healthy aging and their further decline with MCI may account for concomitant declines in SDC. Notably these same sleep features further markedly decline, in concert with declining cognitive function, with the progression to AD. Therefore, progressive changes in sleep quality, architecture, and neural regulation may constitute a contributing factor to cognitive decline that is seen both with healthy aging and, to a much greater extent, with neurodegenerative disease.

Keywords Sleep · Aging · Sleep-dependent memory consolidation · Mild cognitive impairment · Dementia

Contents

1 Introduction

Healthy aging is characterized by changes in sleep, cognitive function, and especially memory as well as in sleep-dependent memory consolidation or SDC (Harand et al. 2012; Pace-Schott and Spencer 2011). Neurodegenerative disorders

are of paramount public health importance in the aging population. It has recently been suggested that, in such disorders, additional impairment in SDC, over and above selective impairments seen in healthy aging (Harand et al. 2012; Pace-Schott and Spencer 2011), may contribute to memory declines that typify such disorders (Rauchs et al. 2008; Westerberg et al. 2010, 2012). In the current chapter, we review changes in sleep quality and physiology seen in healthy aging and in dementia [for comprehensive reviews see (Bliwise 1993, 2011; Petit et al. 2004)]. We then briefly review the scope of cognitive changes seen in healthy aging [for comprehensive reviews see (Grady 2012; Hedden and Gabrieli 2004; Salthouse 2010; Spreng et al. 2010)] as well as changes seen in what, in some elders, constitutes early stages of dementia—mild cognitive impairment (MCI), and especially amnestic MCI or aMCI (Petersen 2004; Petersen and Negash 2008). Finally, we will review age-related changes in sleep-dependent memory processing and how this process might be impacted by MCI.

2 Cognition in Healthy Aging and Mild Cognitive Impairment

2.1 Changes in Cognition with Normal Aging

Healthy aging involves declines in working memory, impairments in forming new episodic memories, and reduced processing speed. However, semantic memory (e.g., vocabulary), autobiographical memory, recognition memory, emotional memory, and priming are spared (Buckner 2004; Drag and Bieliauskas 2010; Grady 2012; Hedden and Gabrieli 2010). Among various neuropsychological tasks showing age-related declines, cross-sectional studies reveal annual declines of approximately 0.02–0.03 standard deviations before age 60 and 0.04–0.05 from age 61 to 96 (Salthouse 2009). Structural and functional neuroimaging studies reveal that age-related changes in frontostriatal systems underlie those cognitive declines whereas spared functions reflect the lesser changes occurring in medial temporal systems (Buckner 2004; Eyler et al. 2011; Hedden and Gabrieli 2010; Kaup et al. 2011). However, it is these medial temporal structures, and in particular the hippocampal formation, that are most impacted in the dementias. Across diverse functional domains, greater recruitment of prefrontal areas (in addition to a number of more posterior lateral cortical areas) in healthy older adults is believed to reflect a compensatory recruitment required to perform tasks that require fewer neural resources in young adults (Davis et al. 2008; Grady 2012; Spreng et al. 2010).

2.2 Changes in Cognition with MCI

MCI represents a condition of elevated risk, relative to the healthy aged population, for progression to a dementing disorder (Ganguli et al. 2011) including Parkinson's

Disease (Goldman and Litvan 2011; Litvan et al. 2012; Rektorova 2011), and Alzheimer's disease (AD) (Albert et al. 2011; Venneri et al. 2011). Diagnosis of MCI requires a cognitive decline that is noticeable by the patient or the patient's family along with below-normative performance on neuropsychological assessments (with an operational threshold of 1.5 SD) but no functional impairment in activities of daily living (Petersen 2004, 2011). MCI can be classified as amnestic MCI (aMCI) if one or more memory domains are impaired (Petersen 2004; Simon et al. 2012) or nonamnestic MCI, the latter being characterized by fewer mnemonic deficits (Petersen 2004; Wang et al. 2012). Memory deficits seen in aMCI include verbal declarative memory (Silva et al. 2012), autobiographical memory (Berna et al. 2012), working memory (Kessels et al. 2011), and prospective memory (Costa et al. 2011) but relative preservation of sequence learning (Nagy et al. 2007). For example, among nondemented individuals presenting to a clinic with subjective memory complaints, those who met criteria for MCI (based upon subjective complaint plus a score 1.5 SD below the age norm on the California Verbal Learning Test) were 3.6 more likely to progress to dementia at an approximately 3-year follow-up (Silva et al. 2012). Inclusion of additional verbal memory tests such as the Weschler Memory Scale-III Logical Memory test improved the sensitivity of the California Verbal Learning Test in predicting subsequent conversion to AD (Rabin et al. 2009). Moreover, a brief test of episodic and semantic verbal memory, the Memory Alteration Test, has been shown to provide good agreement for a diagnosis of aMCI with the 1.5-SD-below-norm criterion obtained from more extensive testing (Rami et al. 2007).

3 Sleep in Healthy Aging and Mild Cognitive Impairment

3.1 Changes in Sleep with Healthy Aging

Healthy aging is accompanied by changes in sleep quality and architecture as well as in the homeostatic and circadian control of sleep propensity [see (Bliwise 2011; Colrain 2011; Dijk et al. 2000; Pace-Schott and Spencer 2011) for reviews]. Prominent changes in sleep quality with aging include decreased total sleep time, increased wake time after sleep onset, and decreased sleep efficiency (Bliwise 2011; Buysse et al. 2005; Huang et al. 2002; O'Donnell et al. 2009). Older adults awaken more frequently and their relative number of awakenings from NREM versus REM is greater than in younger adults (Dijk et al. 2001; Salzarulo et al. 1999). Sleep disruption in the elderly is also exacerbated by nocturia (Asplund and Aberg 1996) and daytime napping (Carskadon et al. 1982). In a study of healthy elders in which longitudinal assessments were begun in either "young–old" individuals (aged 60–74) and "old–old" individuals (75–87) and then followed up at three 1-year intervals, those in the "young–old" group showed little longitudinal change in measures of subjective and laboratory sleep quality (Hoch et al. 1994, 1997).

In contrast, "old–old" individuals showed changes across 3 years in the direction of poorer sleep for sleep efficiency, wake time after sleep onset, and sleep onset latency.

One of the most prominent changes in sleep architecture with aging is a reduction in the deepest stages of nonrapid eye movement (NREM) sleep that is termed slow-wave sleep (SWS) and is also known as NREM stages 3 and 4 or delta sleep. The decline in SWS is paralleled by a reduction in EEG slow-wave activity which is defined as spectral power in the delta (0.5–4.5 Hz) frequency range (Cajochen et al. 2006; Carrier et al. 2001; Ohayon et al. 2004). The decline in SWS with aging is especially prominent in frontal areas of the brain (Munch et al. 2004). With healthy aging, SWS also becomes more distributed across NREM–REM cycles rather than being concentrated in the first one or two NREM–REM cycles of the night as occurs in young adults (Lombardo et al. 1998). Females experience less reduction in SWS with aging than males (Fukuda et al. 1999). Lighter NREM sleep (NREM stages 1 and 2) is increased in proportion to lost SWS. However, in NREM sleep stage 2, specific EEG wave forms characteristic of this sleep stage are reduced: Sleep spindles are reduced in number, density, and amplitude (Carrier et al. 2001; Crowley et al. 2002b; Guazzelli et al. 1986; Landolt et al. 1996; Nicolas et al. 2001; Wauquier 1993; Wei et al. 1999) as are number and amplitude of K-complexes (Crowley et al. 2002a, b). Although the amount of REM sleep declines only slightly with aging (Floyd et al. 2007; Ohayon et al. 2004), the number of rapid eye movements per unit time or "REM density" is decreased (Darchia et al. 2003).

The reductions in deep NREM sleep or SWS as well as the increase in nocturnal awakenings may suggest that the homeostatic sleep drive is damped in older adults (Carrier et al. 2001; Dijk et al. 2010). Nonetheless, homeostatic responses to sleep curtailment or extension remain intact in healthy aging (Cajochen et al. 2006).

The more fragmented and irregular sleep–wake pattern with increased nocturnal awakenings may also suggest a weakening of the circadian clock that controls the daily rhythmicity of sleep as well as of many other physiological processes. Indeed, the master circadian signal from the suprachiasmatic nucleus of the anterior hypothalamus seems to weaken with aging (Hofman and Swaab 2006; Kondratova and Kondratov 2012) resulting in, for example, decreased amplitude of circadian rhythms of objective and subjective sleepiness (Buysse et al. 2005) as well as similar damping in rhythms of core body temperature, melatonin, and cortisol (Dijk et al. 2000; Hofman and Swaab 2006; Kondratova and Kondratov 2012; Monk 2005; Skene and Swaab 2003). Although the sensitivity of the suprachiasmatic nucleus to photic entrainment appears to diminish with age in mammals, including primates (Kondratova and Kondratov 2012), bright light resets the circadian clock similarly in young and older adult humans (Benloucif et al. 2006; Van Someren et al. 2002).

Changes in circadian rhythms with aging can affect human cognition via effects on the circadian timing of sleep, but may also act on cognition-related circadian oscillators in the brain independently of their effects on sleep (Kondratova and Kondratov 2012). The other marked circadian effect of healthy aging is phase

advance of the circadian oscillator that results in an approximately 1 h phase advance of core body temperature, melatonin, and cortisol by around age 65 (Dijk et al. 2000; Duffy et al. 1998; Monk 2005). Nonetheless, the circadian period remains approximately 24.2 h across the lifespan (Czeisler et al. 1999).

3.2 Sleep in MCI and Dementia

Individuals with aMCI report subjective sleep disturbances (Beaulieu-Bonneau and Hudon 2009). While such sleep complaints are not necessarily confirmed by longitudinal actigraphic and diary studies (Westerberg et al. 2010), objective polysomnography indeed reveals that a number of additional sleep changes are characteristic of individuals with MCI over and above changes in sleep seen with healthy aging. For example Westerberg et al. 2012 compared both sleep and memory performance in aMCI patients with age-matched controls. Patients with aMCI showed reduced sleep quality with trends toward lower sleep efficiency and higher wake time after sleep onset. In addition, aMCI patients showed significantly lower duration and percentage of SWS as well as significantly lower EEG spectral power in delta and theta frequency bands during NREM sleep. Moreover, aMCI patients showed significantly reduced spindle counts especially among fast (13–15 Hz) spindles. Interestingly, in these patients, REM sleep was also altered, with trends toward reduced minutes and percentage of REM sleep and increased REM sleep latency as well as a reduction in REM sleep EEG theta power. In the case of nonamnestic MCI, a 2-week actigraphic study revealed greater wake time after sleep onset and more arousals in patients compared with healthy controls (Naismith et al. 2010). Individuals with MCI have also been found to have greater fragmentation of both SWS and REM, the latter being most prominent in ApoE $\varepsilon 4$ carriers (Hita-Yanez et al. 2012a).

With the progression of aMCI to Alzheimer's disease (AD), sleep disturbances become increasingly profound and include increased number and duration of awakenings with concomitant reduction in sleep efficiency and increased amounts of NREM stage 1 sleep beyond that experienced by healthy age-matched controls (Bliwise 1993; McCurry and Ancoli-Israel 2003; Petit et al. 2004). The amount of SWS becomes greatly reduced and NREM stage 2 spindles and K-complexes diminish in frequency, intensity, and morphological integrity (Bliwise 1993; Petit et al. 2004; Rauchs et al. 2008). As the disease further progresses, time in REM sleep also becomes reduced owing to decreased duration of REM episodes, and the overall REM EEG slows due to increased delta and theta power at the expense of alpha and beta (Bliwise 1993; Dykierek et al. 1998; Petit et al. 2004). In addition, compared to age-matched controls, individuals with AD have been shown to have faster mean theta EEG oscillations in REM and SWS (Hot et al. 2011) and to not show the decline in slow-wave sleep across the night displayed by healthy controls (Bonanni et al. 2012).

Among the most striking changes in sleep associated with dementia, particularly AD, is the profound disruption of circadian rhythmicity revealed in symptoms of daytime somnolence, nocturnal waking and "sundowning"—a term describing the exacerbation of agitation late in the day at a time when healthy elders become less active as bedtime nears (Wulff et al. 2010). In AD, there is evidence of prominently delayed sleep phase (Ancoli-Israel et al. 1997) that may be incipient in patients with aMCI (Westerberg et al. 2010).

It has been suggested that cellular neuropathologies (e.g., amyloid plaques and neurofibrillary tangles in AD, Lewy bodies in Parkinson's disease and dementia with Lewy bodies, inclusion bodies in Huntington's disease) accumulate over wakefulness and, conversely, that sleep may inhibit their aggregation (Naidoo 2009). Sleep restriction associated with sleep disorders may, therefore, trigger or advance the onset of neurodegeneration. For instance, the amyloid-ß plaques that underlie AD pathology are increased following experimentally induced sleep deprivation in mice (Kang et al. 2009). Recent findings of increased interstitial fluid and associated metabolite clearance rate during sleep provide a putative mechanism whereby sleep disruption could lead to dementias that, like AD, are associated with abnormal accumulation of endogenous substances (Xie et al. 2013). Additionally, in nondemented older adults, shorter sleep and poorer sleep quality were associated with greater positron emission tomographic estimates of beta-amyloid burden (Spira et al. 2013). Furthermore, sleep loss also triggers the unfolded protein response that, when prolonged, can lead to neuronal death especially in the aging brain (Naidoo 2009).

3.3 Sleep Disturbance as a Predictor of Dementia

A greater degree of sleep disturbances in the elderly may presage increased cognitive impairment at all degrees of cognitive decline ranging from low performance within the normal range to the progression from MCI to AD and other dementias. For example, a large cross-sectional epidemiological study of approximately 3000 individuals over 65 indicated that advanced sleep phase was mildly predictive of lowered cognitive function on the Mini Mental Status Exam (Auyeung et al. 2012). A similarly sized cross-sectional sample of men averaging 76 years of age studied with the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and actigraphy revealed that higher wake time after sleep onset was predictive of poorer performance on the Mini Mental Status Exam and Trails B test (Blackwell et al. 2011a). Likewise, a longitudinal epidemiological study of 1664 cognitively unimpaired elders aged 65–95 showed that elevated scores on the Pittsburgh Sleep Quality Index and habitual sleep duration predicted scores on the Mini Mental Status Exam within the range of cognitive impairment at 12-month follow-up (Potvin et al. 2012). In a large ($n = 663$) longitudinal study of elderly adults (median about 75 years, range 65–94), sleep duration shorter than 6.5 h per night and excessive daytime sleepiness at baseline were found to predict cognitive

decline at 10-year follow-up whereas daytime napping appeared to confer a protective effect (Keage et al. 2012). Likewise, a community-based actigraphic study of 737 nondemented elders showed that greater sleep fragmentation was associated with increased odds of incident AD at follow-up (Lim et al. 2013).

Among neurodegenerative disorders, specific sleep disturbances and disorders may constitute early predictors of progression from prodromal conditions to diagnosed illness. For example, sleep disturbances appearing independently of memory disturbance in individuals with MCI have been shown to predict progression to AD (Hita-Yanez et al. 2012b). Similarly, a prospective study of 300 women with a mean age of 82 years showed that sleep-disordered breathing itself was an independent risk factor for incident MCI or dementia with an adjusted odds ratio of 1.85 (Yaffe et al. 2011). In addition, in a longitudinal community study of over 6000 cognitively intact individuals over age 65, self-reported insomnia independently predicted cognitive decline in males (but not females) at a 3-year follow-up (Cricco et al. 2001).

Poorer sleep quality is also predictive of poorer cognitive performance in nondemented individuals with Parkinson's Disease, although sleep-related impairments were most strongly associated with executive and attentional rather than mnemonic domains (Stavitsky et al. 2012). REM Behavior Disorder (RBD) may represent an early manifestation of neurodegenerative diseases associated with abnormal accumulation of the protein alpha-synuclein (the so-called synucleinopathies which include Parkinson's disease, dementia with Lewy bodies and multisystem atrophy) that presents many years before other symptoms appear and represents damage to pontine structures responsible for REM atonia (Petit et al. 2004; Raggi and Ferri 2010). Interestingly, in a 4-year prospective longitudinal study, RBD was shown to confer a twofold increase in risk of MCI that most likely presaged Parkinson's disease or Lewy Body Dementia (Boot et al. 2012).

3.4 Sleep Disorders and Dementia

Incidence of sleep disorders greatly increases with aging (Ancoli-Israel et al. 2008; Crowley 2011; Neikrug and Ancoli-Israel 2010). Such disorders, and in particular obstructive sleep apnea, may lead to cognitive impairments irrespective of any neurodegenerative process (Blackwell et al. 2011b). Nonetheless, sleep disorders are also extremely prevalent among neurodegenerative diseases as a whole [for reviews see (Petit et al. 2004; Raggi and Ferri 2010)]. Petit et al. (2004) suggest that changes in sleep generally seen across multiple neurodegenerative disorders include sleep fragmentation, increased wake time after sleep onset, disorganization of sleep stages and of the morphology of phasic wave forms such a sleep spindles, and a worsening of sleep symptoms in parallel with worsening waking symptoms.

Elevated incidence of specific sleep disorders have also been shown to accompany specific neurodegenerative diseases. For example increased incidence of sleep-disordered breathing accompanies AD, Parkinson's disease, and multisystem

atrophy. Similarly, increased incidence of periodic limb movement disorder is seen in Parkinson's disease, multisystem atrophy, and spinocerebellar ataxia (Raggi and Ferri 2010). Restless Leg Syndrome also often accompanies Parkinson's disease and spinocerebellar ataxia (Petit et al. 2004; Raggi and Ferri 2010; Wong et al. 2014). Disturbances of REM are especially common in the synucleopathies as noted above, but also occur in AD (Bliwise 1993; Dykierek et al. 1998; Petit et al. 2004).

4 Sleep-Dependent Memory Consolidation in Healthy Aging and Mild Cognitive Impairment

4.1 Changes in Sleep-Dependent Memory Consolidation with Normal Aging

Memories are consolidated offline. Processing of memories when no longer engaged in learning is termed memory consolidation. Consolidation refers to both the stabilization and strengthening of memory traces between encoding and subsequent recall (Diekelmann and Born 2010; Diekelmann et al. 2009). While consolidation can occur over wake, in healthy young adults consolidation is optimized over sleep through a process termed sleep-dependent memory consolidation (SDC). A wealth of studies suggest that performance on a wide range of learning tasks is benefited by SDC in healthy young adults and these findings have been extensively reviewed (Diekelmann and Born 2010; Diekelmann et al. 2009; Stickgold 2005; Walker 2009). For instance, recall of a declarative memory task, such as word-pair learning is greater following an interval with sleep relative to recall following an equivalent interval spent awake (Plihal and Born 1997, 1999; Rasch et al. 2007; Tucker et al. 2006). Moreover, SDC has been shown to render prior memories resistant to interference from new encoding following sleep (Ellenbogen et al. 2006). Young adults also benefit from sleep following procedural learning. For instance, Walker et al. (2002) and others (Fischer et al. 2002; Spencer et al. 2006, 2007) have illustrated as much as 18 % enhancement on a motor-sequence learning task following sleep. Likewise, Djonlagic et al. 2009 demonstrated sleep-related improvements on the Weather Prediction Task, thought to be a form of nonmotor procedural learning (Gluck et al. 2002).

Only recently have studies turned to changes in sleep-dependent consolidation across the lifespan [for reviews, see (Diekelmann et al. 2009; Kopasz et al. 2010; Pace-Schott and Spencer 2011)]. Hornung et al. 2005 predicted a relationship between the reduction in memory and the changes in sleep that occur with aging. According to this theoretical paper, reductions in sleep and memory may share a common source such as reduced brain volume or neurochemical changes. Conversely, the relationship may be direct: Changes in sleep—such as reduced SWS, REM, or spindle density—may result in reduced memory.

Buckley and Schatzberg (2005) similarly predicted a relationship between sleep and memory declines with aging. Specifically they posited that changes in the hypothalamo-pituitary-adrenal (HPA) axis in older adults underlie the reduction in sleep quality and, thereby, the reduction of memory in older adults. The HPA axis is a feedback loop that controls the stress response and other processes via cortisol release. Cortisol also fluctuates in a circadian rhythm with a peak in the morning and falling throughout the day to an evening nadir. The circadian rhythm is flattened in older adults and the HPA axis becomes hyperactive. The combination of these two changes, according to Buckley and Schatzberg (2005), results in the age-related changes in sleep that, in turn, reduce SDC.

Notably, this theoretical work preceded empirical studies of SDC in older adults. In the first direct test of whether older adults preferentially consolidate learning over a period of sleep, we compared sleep-dependent performance changes over sleep and wake in older (45–80 years) and younger adults (18–24 years) adults (Spencer et al. 2007). The task was a motor-sequence learning task, a variant of the serial reaction time paradigm introduced by Nissen and Bullemer (1987). Participants learned a sequence of finger movements by making a key press in response to the spatial position of visual stimuli presented on a computer monitor. Stimuli appeared in a repeating sequence of locations with occasional presentations of randomized stimuli that allowed sequence versus general learning to be differentiated. In young adults, performance on the motor-sequence learning task is greatest following an interval with sleep relative to an interval of wake (Spencer et al. 2006), [see also (Robertson et al. 2004; Walker et al. 2002)]. However, performance changes in the older adult group following an overnight interval with sleep did not differ from performance changes following a daytime interval spent awake. Moreover, there was no difference in initial learning between younger and older individuals regardless of the time of day at which they were tested indicating that the observed changes were not due to circadian influences on performance. Hence, the added benefit to motor-sequence learning accrued from posttraining sleep in younger adults was unavailable to older adults [see also (Siengsukon and Boyd 2008, 2009)]. Recently, Tucker argued that the lack of over-sleep performance changes reported in these studies was due to complexity causing a dramatic drop at immediate retest that is reduced by late retest (Tucker et al. 2011). Whether this is the case is unclear. In reexamining our data (Spencer et al. 2006), we did not see a similar drop in performance in immediate retest (unpublished data). We note, too, that baseline differences in the older adult wake and sleep groups and lack of a young adult sleep group limit such conclusions (Tucker et al. 2011). Likewise, Peters et al. 2008b noted a dip in immediate retest performance using a pursuit rotor task, another test of motor procedural learning. In spite of this, they found reduced over-sleep consolidation in older relative to young adults.

Performance on motor-sequence learning tasks can be decomposed into goal (perceptual)- and motor-based components and, among young adults, sleep selectively benefits goal-based learning (Cohen et al. 2005). However sleep no

longer enhances goal-based learning in older adults, suggesting that loss of sleep benefit to this component of motor learning underlies the more general deficit (Pace-Schott and Spencer 2013).

With respect to declarative learning, the picture is clearer: A number of recent studies suggest that SDC is preserved in older adults for declarative learning tasks. Aly and Moskovitch (2010) compared episodic recall following an interval with overnight sleep relative to recall following a daytime interval spent awake. While older adults (69–80 years) exhibited greater forgetting over both intervals relative to the young adult group (19–29 years), the protection of the memory provided by sleep, did not differ across the age groups. Recently, we directly compared SDC for declarative and procedural learning tasks in young (20–34 years), middle-aged (35–50 years), and older adults (51–70 years) (Wilson et al. 2012). The declarative task was a word-pair learning task using semantically unassociated word pairs. The procedural learning task was the serial reaction time task of our earlier work described above (Spencer et al. 2006). We again found an age-related decrease in SDC of the procedural task and this decline was evident even in the middle-aged group. Importantly, we also found, in the same participants, spared SDC in older adults on the word-pair learning task. While sleep physiology was not available, this contrast defies simple explanations based on physiological changes in sleep with age. In young adults, declarative memory consolidation has largely been associated with time spent in SWS (Diekelmann and Born 2010; Diekelmann et al. 2009) while procedural memory consolidation is associated with time in NREM stage 2 (Walker et al. 2002) or REM (Plihal and Born 1997). Based on a simple sleep physiological account, then, one would expect that sleep-dependent consolidation would be reduced for declarative memories given the drastic reduction in SWS with age. Indeed, some studies suggest that SWS reductions with aging are linked with diminished SDC of verbal declarative memory (Backhaus et al. 2007; Scullin 2013). In contrast, age-related changes in sleep would predict that consolidation of procedural learning would be relatively spared given the abundance or even increase in NREM stage 2 and relative sparing of REM. Thus, a more complex physiological association may underlie the specific reduction in procedural memory consolidation over sleep with age. For instance, although preserved, sleep stages such as NREM stage 2 and REM are more fragmented in older adults. Such fragmentation is associated with reduced consolidation in young adults with sleep apnea (Djonlagic et al. 2012).

Another question is whether the maintained sleep benefit to verbal declarative memory seen in older adults also extends to visuospatial declarative memory. A recent study suggests that perhaps this is not the case (Cherdieu et al. 2014). Relative to waking, forgetting of visuospatial learning in a stimulus-location task was reduced following a night's sleep in young adults, whereas forgetting across wake and sleep did not differ in older adults. Although requiring replication, this finding suggests that sleep benefit in the verbal domain of declarative memory may be especially protected during healthy aging.

4.2 Sleep Physiological Correlates of Sleep-Dependent Memory Consolidation with Normal Aging

In young adults, raw numbers and numbers per unit time (density) of sleep spindles increase following learning on both procedural and declarative memory tasks [see (Fogel and Smith 2011) for a review]. This increase in spindles correlates with memory performance for such learning measured after sleep (Fogel and Smith 2011). Moreover, baseline measures of spindle numbers and density predict performance on specific tasks as well as measures of general cognitive capacity (Fogel and Smith 2011). Given that spindles are known to decrease in number, density, and amplitude with aging (see above), their role in age-related decline in SDC is a topic of increasing interest. For example, in older adults, greater spindle density has been linked with better performance on a variety of neuropsychological tests including a verbal memory task, indicating that spindle density continues to reflect neuronal integrity into older age (Lafortune et al. 2013).

One recent study in older females (average about 68 years) has shown that SDC of a nonverbal declarative visual memory task (Rey-Osterreith complex figure) was indeed correlated with higher numbers and density of sleep spindles on the night following learning (Seeck-Hirschner et al. 2012). However, this study did not compare spindle density during the postlearning night to baseline spindle density and, therefore, both performance and spindle density might reflect a third variable such as trait sleep quality or IQ (Fogel and Smith 2011).

In a second study, the relationship between sleep spindles and SDC was examined using a procedural learning task (pursuit rotor) that was learned in the afternoon following a baseline PSG night in a group of young (17–24 years) and older (62–79 years) adults (Peters et al. 2008a). Both groups were then retested 1 week later. Although both groups performed significantly better at 1 week retest, only the young adults showed significant increase in number of sleep spindles at the posttesting relative to the baseline night. Additionally, in the young but not older adults, performance at initial learning was significantly correlated with this post-training increase in spindles whereas performance at retest was negatively correlated with increased spindles, an effect these authors attribute to a ceiling effect. However, in a few older individuals, improvement at retest accompanied spindle density increases resulting in a trend toward a positive correlation suggesting that, in those older adults for whom a postlearning spindle increase is preserved, SDC may also be enhanced. Additionally, when groups were compared using percentage increase following learning, group differences in spindle density and performance improvement were no longer significant. Therefore, as Peters et al. (2008a) suggest, sleep and spindles may enhance motor memory consolidation with greater inter-individual variability in older versus younger adults. As these authors also note, studies showing dose-dependent effects of graded amounts of motor learning on subsequent spindle density are needed before causal inferences can be made. Similarly, wake controls are necessary to attribute performance enhancement to

offline processes that include sleep rather than offline processes more generally [for a discussion, see (Robertson 2009)].

An early study hypothesized that the global organization of sleep rather than specific sleep stages would promote declarative memory consolidation in elderly adults (Mazzoni et al. 1999). These investigators presented two sets of 20 unrelated word pairs to 30 healthy older adults (mean 68 year) twice, once with a 10-min delay before testing to assess baseline verbal recall ability and the other prior to a night of sleep with testing the following morning. Sleep cycles were operationally defined as a sequence of REM and NREM uninterrupted by any waking period >2 min. Memory performance following sleep was positively correlated with the mean duration of sleep cycles as well as the proportion of total sleep time spent in these cycles but not with any other sleep parameter. The investigators hypothesized that sleep cycle duration allows sequential processes requiring more than a single sleep stage, such as the protein synthesis necessary for memory consolidation to take place. This latter finding may explain why greater fragmentation of NREM stage 2 in older adults (see above) as well sleep fragmentation brought about by mild sleep apnea (Djonlagic et al. 2012) may impact sleep-dependent procedural learning.

4.3 Neural Correlates of Sleep-Dependent Memory Consolidation with Normal Aging

A recent functional magnetic resonance imaging (fMRI) study illustrates that memory encoding in older relative to younger adults results in a different relationship between preceding sleep quality and task-related regional brain recruitment (Jonelis et al. 2012). In older but not younger adults, a verbal encoding task produced a positive relationship between total sleep time on the preceding night and bilateral anterior parahippocampal activation. In contrast, these authors showed that this same task, in younger adults, produced a negative, unilateral relationship between activation of this region and preceding sleep duration. These authors explain this difference in reference to a model of hemispheric asymmetry reduction in older adults that posits a compensatory bilateral recruitment of structures in older adults by mnemonic tasks that, in younger adults, can be performed unihemispherically (Cabeza 2002).

More recently, combined EEG and fMRI studies have linked age-related brain structural and functional changes with the associations between sleep architecture and memory. In the case of declarative memory, age-related reductions in sleep spindle density predicted both impairment on a visual memory task and diminished hippocampal activation during the learning phase of this task (Mander et al. 2013a). Specifically, fast sleep spindles, which are preferentially expressed at frontal sites, predicted the observed declines implicating prefrontal processes in age-related cognitive decline. Similarly, age-related decline in slow-wave activity was linked to

reduced medial prefrontal volume, diminished hippocampal-prefrontal connectivity, and impaired performance on a verbal memory task (Mander et al. 2013b). In the case of procedural learning, sleep-dependent consolidation of motor-sequence memory was associated with both greater spindle density and greater striatal activation in younger compared with older healthy adults (Fogel et al. 2013). Notably, these anatomical associations correspond well with the known anatomical bases of declarative and procedural memory systems (Mesulam 2000) as well as the prefrontal focus of reductions in structure and function accompanying healthy aging (Buckner 2004; Hedden and Gabrieli 2004).

REM sleep is facilitated by cholinergic neurotransmission [reviewed in (Pace-Schott and Hobson 2002)]. The neuropathology of AD produces both widespread cholinergic deficits (Terry and Buccafusco 2003) and reduced REM percent (Petit et al. 2004). This, combined with the modest decrease in REM percent (Ohayon et al. 2004) and density (Darchia et al. 2003) with healthy aging, has led some investigators to examine whether such age-related REM decreases may account for age-related decreases in SDC [e.g., (Hornung et al. 2006; Schredl et al. 2001)]. For example Schredl et al. 2001 showed that, when REM was enhanced in healthy individuals aged 58–78 years using donepezil [see also (Schredl et al. 2006)], the degree of overnight improvement on a verbal learning task correlated with the degree to which REM was enhanced. However, in this study, the lack of a wake control group as well as practice effects due to repeated stimuli precluded identifying the direct effects of pharmacological REM enhancement on memory consolidation. In a follow-up study (Hornung et al. 2007), these authors investigated the effects of REM manipulations in healthy older adults aged 60–85 years on both a declarative memory (paired associates learning) and a procedural (mirror tracing) task. These investigators compared the effects of both pharmacological (donepezil) and instrumental (REM sleep deprivation followed by rebound) REM sleep augmentation to a placebo group that was allowed to sleep without intervention. Additionally, performance of a group with instrumental REM sleep deprivation was compared to a group receiving a similar frequency of instrumental NREM stage 2 awakenings. Despite achieving a high degree of differentiation in both tonic and phasic REM sleep between groups, only with pharmacological enhancement of REM sleep was there significantly improved morning performance and improvement was seen only for the procedural memory task. Interestingly, total and phasic REM sleep time had an opposite relationship to procedural memory performance (positive and negative respectively). Moreover, the elimination half-life of donepezil potentially allowed its acute effects to influence morning performance in the pharmacological enhancement group. These investigators, therefore, concluded that, although REM sleep is positively associated with consolidation of procedural learning, it may have been cholinergic stimulation rather than REM sleep duration per se that enhanced such consolidation. It is notable that in young adults, pharmacological suppression of REM sleep by a selective serotonin reuptake inhibitor augmented rather than impeded consolidation of a similar procedural memory task (Rasch et al. 2009).

4.4 Changes in Sleep-Dependent Memory Consolidation with Sleep Disorders

As with general cognitive impairment, sleep disorders may impair SDC in the absence of any clear neurodegenerative disorder or dementia [for a review, see (Cipolli et al. 2013)]. For example middle-aged (average about 41 years) individuals with primary insomnia showed diminished consolidation of declarative memory (word pairs) relative to controls but preserved sleep-dependent consolidation of procedural (mirror tracing) learning (Backhaus et al. 2006). In contrast, in middle-aged (average about 46 years) subjects, Nissen et al. (2010) found that, unlike good sleeper controls, patients with primary insomnia who slept versus those who remained awake, showed neither greater percent improvement on the mirror-tracing task nor enhanced retention of declarative learning on the visual verbal task. Both studies, however, demonstrate that primary insomnia can negatively impact SDC in otherwise healthy middle-aged adults.

Djonlagic et al. (2012) showed, in young to middle-aged adults (average about 30 years), that the arousals associated with even mild obstructive sleep apnea can lead to diminished SDC of procedural memory (motor-sequence learning task) despite otherwise similar sleep architecture. Moreover, in this study, it was the arousal index (indicative of sleep fragmentation) rather than oxygen desaturation that predicted decrement in offline consolidation. Similarly, middle-aged (average about 47 years) patients with moderate obstructive sleep apnea displayed significantly lower overnight retention of both verbal and visual declarative memory (visual and verbal memory task) as well as procedural (mirror tracing) memory relative to normally sleeping controls (Kloepfer et al. 2009).

In narcolepsy with cataplexy, there is also evidence of reduced SDC on a texture discrimination task (Cipolli et al. 2009) that has been widely shown to demonstrate SDC in normal controls (Stickgold 2005). Cipolli et al. (2009) attributed poorer sleep-dependent improvement on the texture discrimination task to the greater fragmentation and poorer organization of sleep architecture in narcolepsy. Notably, in this study, overnight improvement in texture discrimination performance was poorest in those narcoleptic individuals with the greatest degree of sleep disorganization.

4.5 Sleep-Dependent Consolidation in aMCI

Bearing in mind the potential interactions between aging, sleep disorders, and cognitive impairment, studies of SDC can be carried out at early stages of neurodegenerative disorders when functional impairment is minimal and research participants are able to understand instructions in a manner comparable to healthy older adults [e.g., (Westerberg et al. 2010, 2012)]. For example, in a 2-week actigraphic study (Westerberg et al. 2010), 10 individuals with aMCI and 10 age-matched

controls were compared using a daily encoding and short-term recognition task (continuous recognition task) that provided mixed verbal and nonverbal stimuli that were tested for recognition memory 24 h later (24-h recognition) before encoding a new set of stimuli. Individuals with aMCI performed more poorly than controls on 24-h recognition and on both outcome variables from the continuous recognition task (detection of a second presentation during encoding and a short-term delayed recognition test). Day-to-day variability was greater in aMCI relative to controls for all three recognition memory measures as well as for actigraphic measures of sleep (although there were no overall group differences in actigraphic or subjective diary sleep parameters). Most notably, objective (actigraphic) and subjective (diary) sleep quality in aMCI but not control participants was predictive of better performance on the 24-h recognition task—i.e., the measure that relied on overnight retention of material learned the previous day. The fact that continuous recognition measures were not similarly predicted by the previous night's sleep quality suggests that it was this overnight retention and not more general effects of poor sleep that was impaired following nights with poorer sleep in aMCI.

These investigators went on to compare performance changes across sleep, between aMCI and age-matched controls, on tests of verbal recall (related paired associates), recognition of previously learned facts, and implicit recognition memory for previously viewed versus novel objects (Westerberg et al. 2012). Whereas normal controls significantly improved paired associates recall over sleep relative to their performance shortly following encoding the previous evening, those with aMCI showed a significant decrease. That this difference was specifically attributable to sleep was indicated by the fact that the two groups did not differ in recall performance on the previous evening following encoding. Moreover, both groups showed similar, positive correlations of overnight memory performance with delta and theta spectral power during both NREM sleep and REM sleep (although these correlations were significant only in controls during NREM sleep). These investigators concluded that aMCI pathology can diminish SDC over and above declines attributable to normal aging.

Rauchs et al. (2008) compared both sleep physiology and SDC in individuals who had progressed beyond MCI to an actual diagnosis of mild AD with age-matched, older healthy controls as well as with young adults. Individuals with AD showed poorer memory retention over sleep than both young and older controls despite having been trained to a similar level of presleep performance. Compared to young adults, the older groups (control and AD) showed the expected decrease in SWS, REM, and both fast and slow spindle counts and intensity. Compared with older controls, AD patients showed a significant, specific decrease in numbers of fast spindles. Moreover, among the AD patients, the intensity of both total and fast spindles was associated with short-term recall ability. These investigators therefore suggest that, in AD, spindle intensity may reflect the current integrity of memory-related structures with fewer spindles associated with greater neurodegeneration (Rauchs et al. 2008). Other changes in sleep architecture related to memory consolidation in normal aging versus AD include faster theta-range oscillations during REM and slow-wave sleep following a learning task (Hot et al. 2011).

This change was interpreted as a compensatory response since faster theta oscillations were also associated with better memory performance.

SDC has also been examined in individuals with functional memory disorder, a psychogenic, stress-related condition believed to produce memory impairments without MCI or dementia (Puetz et al. 2011). In a group of such individuals (average about 52 years), sleep-dependent consolidation of declarative memory on the visual verbal task was impaired relative to matched controls. These investigators hypothesize that cortical hyperarousal in functional memory disorder may interfere with sleep-dependent consolidation of declarative memory in these individuals. Their findings suggest that a variety of functional abnormalities in the central nervous system may impair SDC even in the absence of definite neurodegeneration.

5 Conclusions

In healthy aging, numerous studies have shown an association of changes in sleep quality and architecture with changes in cognition. Nonetheless, causal factors in this association are not yet clear. Changes in sleep-dependent memory consolidation due to age-related changes in specific sleep stages such as SWS or REM or phasic events such as spindles and REMs constitute strong candidates as contributors to this association. Emerging findings are now able to associate these linkages between behavior and sleep architecture to structural and functional changes in the brain (Fogel et al. 2013; Mander et al. 2013a, b), and particularly the changes in frontal systems known to typify healthy aging (Hedden and Gabrieli 2004). Clearly, sleep disorders, in otherwise healthy individuals, can exacerbate age-related changes in cognition including changes in SDC. When cognitive changes are sufficiently severe to diagnose MCI, additional changes in sleep architecture and circadian rhythmicity that are related to the underlying pathology, may further disrupt sleep. These may, in turn, further exacerbate cognitive decline through diminished SDC. Among such sleep features that potentially contribute to decreased memory consolidation, the NREM sleep features of SWS and spindles, that both are diminished in healthy aging and further so in MCI, seem most likely to be involved in cognitive decline. In contrast, the declines in REM sleep, that are minimal in healthy aging but apparent in AD, may be less involved at early stages of memory impairment due to neurodegenerative disease. Nonetheless change in REM sleep, specifically the loss of atonia leading to RBD, constitutes one of the clearest sleep-related predictors of synucleopathies that, in their early stages, can present as MCI. The study of SDC potentially constitutes a window into the effects of both healthy aging and aging with neurodegeneration on cognitive integrity.

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References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement J Alzheimer's Assoc 7:270–279

Aly M, Moscovitch M (2010) The effects of sleep on episodic memory in older and younger adults. Mem 1–8

Ancoli-Israel S, Ayalon L, Salzman C (2008) Sleep in the elderly: normal variations and common sleep disorders. Harv Rev Psychiatry 16:279–286

Ancoli-Israel S, Klauber MR, Jones DW, Kripke DF, Martin J et al (1997) Variations in circadian rhythms of activity, sleep, and light exposure related to dementia in nursing-home patients. Sleep 20:18–23

Asplund R, Aberg H (1996) Nocturnal micturition, sleep and well-being in women of ages 40–64 years. Maturitas 24:73–81

Auyeung TW, Lee JS, Leung J, Kwok T, Leung PC et al (2012) Cognitive deficit is associated with phase advance of sleep-wake rhythm, daily napping, and prolonged sleep duration-a cross-sectional study in 2,947 community-dwelling older adults. Age (Dordr)

Backhaus J, Born J, Hoeckesfeld R, Fokuhl S, Hohagen F, Junghanns K (2007) Midlife decline in declarative memory consolidation is correlated with a decline in slow wave sleep. Learn Mem 14:336–341

Backhaus J, Junghanns K, Born J, Hohaus K, Faasch F, Hohagen F (2006) Impaired declarative memory consolidation during sleep in patients with primary insomnia: Influence of sleep architecture and nocturnal cortisol release. Biol Psychiatry 60:1324–1330

Beaulieu-Bonneau S, Hudon C (2009) Sleep disturbances in older adults with mild cognitive impairment. Int Psychogeriatr 21:654–666

Benloucif S, Green K, L'Hermite-Baleriaux M, Weintraub S, Wolfe LF, Zee PC (2006) Responsiveness of the aging circadian clock to light. Neurobiol Aging 27:1870–1879

Berna F, Schonknecht P, Seidl U, Toro P, Schroder J (2012) Episodic autobiographical memory in normal aging and mild cognitive impairment: a population-based study. Psychiatry Res 200(2–3):807–812

Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE et al (2011a) Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. Sleep 34:1347–1356

Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE et al (2011b) Associations between sleep architecture and sleep-disordered breathing and cognition in older community-dwelling men: the osteoporotic fractures in men sleep study. J Am Geriatr Soc 59:2217–2225

Bliwise D (2011) Normal aging. In: Kryger MH, Roth T, Dement WC (ed) Principles and practice of sleep medicine, 5th edn. Elsevier, Philadelphia

Bliwise DL (1993) Sleep in normal aging and dementia. Sleep 16:40–81

Bonanni E, Di Coscio E, Maestri M, Carnicelli L, Tsekou H et al (2012) Differences in EEG delta frequency characteristics and patterns in slow-wave sleep between dementia patients and controls: a pilot study. J Clin Neurophysiol 29:50–54

Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE et al (2012) Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. Ann Neurol 71:49–56

Buckley TM, Schatzberg AF (2005) Aging and the role of the HPA axis and rhythm in sleep and memory-consolidation. Am J Geriatr Psychiatry 13(5):344–352

Buckner RL (2004) Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44:195–208

Buysse DJ, Monk TH, Carrier J, Begley A (2005) Circadian patterns of sleep, sleepiness, and performance in older and younger adults. Sleep 28:1365–1376

Cabeza R (2002) Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychol Aging 17(1):85–100
Cajochen C, Munch M, Knoblauch V, Blatter K, Wirz-Justice A (2006) Age-related changes in the circadian and homeostatic regulation of human sleep. Chronobiol Int 23:461–474
Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH (2001) The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). Psychophysiology 38:232–242
Carskadon MA, Brown ED, Dement WC (1982) Sleep fragmentation in the elderly: relationship to daytime sleep tendency. Neurobiol Aging 3:321–327
Cherdieu M, Reynaud E, Uhlrich J, Versace R, Mazza S (2014) Does age worsen sleep-dependent memory consolidation? J Sleep Res 23:53–60
Cipolli C, Campana G, Campi C, Mattarozzi K, Mazzetti M et al (2009) Sleep and time course of consolidation of visual discrimination skills in patients with narcolepsy-cataplexy. J Sleep Res 18:209–220
Cipolli C, Mazzetti M, Plazzi G (2013) Sleep-dependent memory consolidation in patients with sleep disorders. Sleep Med Rev 17(2):91–103
Cohen DA, Pascual-Leone A, Press DZ, Robertson EM (2005) Off-line learning of motor skill memory: a double dissociation of goal and movement. Proc Natl Acad Sci U S A 102: 18237–18241
Colrain IM (2011) Sleep and the brain. Neuropsychol Rev 21:1–4
Costa A, Caltagirone C, Carlesimo GA (2011) Prospective memory impairment in mild cognitive impairment: an analytical review. Neuropsychol Rev 21:390–404
Cricco M, Simonsick EM, Foley DJ (2001) The impact of insomnia on cognitive functioning in older adults. J Am Geriatr Soc 49:1185–1189
Crowley K (2011) Sleep and sleep disorders in older adults. Neuropsychol Rev 21:41–53
Crowley K, Trinder J, Colrain IM (2002a) An examination of evoked K-complex amplitude and frequency of occurrence in the elderly. J Sleep Res 11:129–140
Crowley K, Trinder J, Kim Y, Carrington M, Colrain IM (2002b) The effects of normal aging on sleep spindle and K-complex production. Clin Neurophysiol 113:1615–1622
Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF et al (1999) Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 284:2177–2181
Darchia N, Campbell IG, Feinberg I (2003) Rapid eye movement density is reduced in the normal elderly. Sleep 26:973–977
Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R (2008) Que PASA? The posterior-anterior shift in aging. Cereb Cortex 18:1201–1209
Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev 11:114–126
Diekelmann S, Wilhelm I, Born J (2009) The whats and whens of sleep-dependent memory consolidation. Sleep Med Rev 13:309–321
Dijk DJ, Duffy JF, Czeisler CA (2000) Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. Chronobiol Int 17:285–311
Dijk DJ, Duffy JF, Czeisler CA (2001) Age-related increase in awakenings: impaired consolidation of nonREM sleep at all circadian phases. Sleep 24:565–577
Dijk DJ, Groeger JA, Stanley N, Deacon S (2010) Age-related reduction in daytime sleep propensity and nocturnal slow wave sleep. Sleep 33:211–223
Djonlagic I, Rosenfeld A, Shohamy D, Myers C, Gluck M, Stickgold R (2009) Sleep enhances category learning. Learn Mem 16:751–755
Djonlagic I, Saboisky J, Carusona A, Stickgold R, Malhotra A (2012) Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. PLoS ONE 7:e34106
Drag LL, Bieliauskas LA (2010) Contemporary review 2009: cognitive aging. J Geriatr Psychiatry Neurol 23:75–93
Duffy JF, Dijk DJ, Klerman EB, Czeisler CA (1998) Later endogenous circadian temperature nadir relative to an earlier wake time in older people. Am J Physiol 275:R1478–R1487

Dykierek P, Stadtmuller G, Schramm P, Bahro M, van Calker D et al (1998) The value of REM sleep parameters in differentiating Alzheimer's disease from old-age depression and normal aging. J Psychiatr Res 32:1–9

Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL (2006) Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. Curr Biol 16:1290–1294

Eyler LT, Sherzai A, Kaup AR, Jeste DV (2011) A review of functional brain imaging correlates of successful cognitive aging. Biol Psychiatry 70:115–122

Fischer S, Hallschmid M, Elsner AL, Born J (2002) Sleep forms memory for finger skills. Proc Natl Acad Sci U S A 99:11987–11991

Floyd JA, Janisse JJ, Jenuwine ES, Ager JW (2007) Changes in REM-sleep percentage over the adult lifespan. Sleep 30:829–836

Fogel SM, Albouy G, Vien C, Popovicci R, King BR et al (2013) fMRI and sleep correlates of the age-related impairment in motor memory consolidation. Hum Brain Mapp doi: 10.1002/hbm.22426. [Epub ahead of print]

Fogel SM, Smith CT (2011) The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35:1154–1165

Fukuda N, Honma H, Kohsaka M, Kobayashi R, Sakakibara S et al (1999) Gender difference of slow wave sleep in middle aged and elderly subjects. Psychiatry Clin Neurosci 53:151–153

Ganguli M, Snitz BE, Saxton JA, Chang CC, Lee CW et al (2011) Outcomes of mild cognitive impairment by definition: a population study. Arch Neurol 68:761–767

Gluck MA, Shohamy D, Myers C (2002) How do people solve the "weather prediction" task? Individual variability in strategies for probabilistic category learning. Learn Mem 9:408–418

Goldman JG, Litvan I (2011) Mild cognitive impairment in Parkinson's disease. Minerva Med 102:441–459

Grady C (2012) The cognitive neuroscience of ageing. Nat Rev 13:491–505

Guazzelli M, Feinberg I, Aminoff M, Fein G, Floyd TC, Maggini C (1986) Sleep spindles in normal elderly: comparison with young adult patterns and relation to nocturnal awakening, cognitive function and brain atrophy. Electroencephalogr Clin Neurophysiol 63:526–539

Harand C, Bertran F, Doidy F, Guenole F, Desgranges B et al (2012) How aging affects sleep-dependent memory consolidation? Front Neurol 3:8

Hedden T, Gabrieli JD (2010) Shared and selective neural correlates of inhibition, facilitation, and shifting processes during executive control. Neuroimage 51:421–431

Hedden T, Gabrieli JD (2004) Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev 5:87–96

Hita-Yanez E, Atienza M, Gil-Neciga E, Cantero JL (2012a) Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and ApoE epsilon4 genotype. Curr Alzheimer Res 9:290–297

Hita-Yanez E, Atienza M, Gil-Neciga E, Cantero JL (2012b) Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and ApoE varepsilon4 genotype. Curr Alzheimer Res 9:290–297

Hoch CC, Dew MA, Reynolds CF 3rd, Buysse DJ, Nowell PD et al (1997) Longitudinal changes in diary- and laboratory-based sleep measures in healthy "old–old" and "young–old" subjects: a three-year follow-up. Sleep 20:192–202

Hoch CC, Dew MA, Reynolds CF 3rd, Monk TH, Buysse DJ et al (1994) A longitudinal study of laboratory- and diary-based sleep measures in healthy "old–old" and "young–old" volunteers. Sleep 17:489–496

Hofman MA, Swaab DF (2006) Living by the clock: the circadian pacemaker in older people. Ageing Res Rev 5:33–51

Hornung OP, Danker-Hopfe H, Heuser I (2005) Age-related changes in sleep and memory: commonalities and interrelationships. Exp Gerontol 40:279–285

Hornung OP, Regen F, Danker-Hopfe H, Schredl M, Heuser I (2007) The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. Biol Psychiatry 61:750–757

Hornung OP, Regen F, Schredl M, Heuser I, Danker-Hopfe H (2006) Manipulating REM sleep in older adults by selective REM sleep deprivation and physiological as well as pharmacological REM sleep augmentation methods. Exp Neurol 197:486–494

Hot P, Rauchs G, Bertran F, Denise P, Desgranges B et al (2011) Changes in sleep theta rhythm are related to episodic memory impairment in early Alzheimer's disease. Biol Psychol 87:334–339

Huang YL, Liu RY, Wang QS, Van Someren EJ, Xu H, Zhou JN (2002) Age-associated difference in circadian sleep-wake and rest-activity rhythms. Physiol Behav 76:597–603

Jonelis MB, Drummond SP, Salamat JS, McKenna BS, Ancoli-Israel S, Bondi MW (2012) Age-related influences of prior sleep on brain activation during verbal encoding. Front Neurol 3:49

Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP et al (2009) Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 326:1005–1007

Kaup AR, Mirzakhanian H, Jeste DV, Eyler LT (2011) A review of the brain structure correlates of successful cognitive aging. J Neuropsychiatry Clin Neurosci 23:6–15

Keage HA, Banks S, Yang KL, Morgan K, Brayne C, Matthews FE (2012) What sleep characteristics predict cognitive decline in the elderly? Sleep Med 13(7):886–892

Kessels RP, Molleman PW, Oosterman JM (2011) Assessment of working-memory deficits in patients with mild cognitive impairment and Alzheimer's dementia using Wechsler's working memory index. Aging Clin Exp Res 23:487–490

Kloepfer C, Riemann D, Nofzinger EA, Feige B, Unterrainer J et al (2009) Memory before and after sleep in patients with moderate obstructive sleep apnea. J Clin Sleep Med 5:540–548

Kondratova AA, Kondratov RV (2012) The circadian clock and pathology of the ageing brain. Nat Rev 13:325–335

Kopasz M, Loessl B, Hornyak M, Riemann D, Nissen C et al (2010) Sleep and memory in healthy children and adolescents—a critical review. Sleep Med Rev 14:167–177

Lafortune M, Gagnon JF, Martin N, Latreille V, Dube J et al (2013) Sleep spindles and rapid eye movement sleep as predictors of next morning cognitive performance in healthy middle-aged and older participants. J Sleep Res doi: 10.1111/jsr.12108. [Epub ahead of print]

Landolt HP, Dijk DJ, Achermann P, Borbely AA (1996) Effect of age on the sleep EEG: slow-wave activity and spindle frequency activity in young and middle-aged men. Brain Res 738:205–212

Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA (2013) Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. Sleep 36:1027–1032

Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D et al (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. Mov Disord 27:349–356

Lombardo P, Formicola G, Gori S, Gneri C, Massetani R et al (1998) Slow wave sleep (SWS) distribution across night sleep episode in the elderly. Aging (Milano) 10:445–448

Mander BA, Rao V, Lu B, Saletin JM, Ancoli-Israel S et al (2013a) Impaired prefrontal sleep spindle regulation of hippocampal-dependent learning in older adults. Cereb Cortex doi: 10.1093/cercor/bht188 [Epub ahead of print]

Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR et al (2013b) Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. Nat Neurosci 16:357–364

Mazzoni G, Gori S, Formicola G, Gneri C, Massetani R et al (1999) Word recall correlates with sleep cycles in elderly subjects. J Sleep Res 8:185–188

McCurry SM, Ancoli-Israel S (2003) Sleep dysfunction in Alzheimer's disease and other dementias. Curr Treat Options Neurol 5:261–272

Mesulam M-M (2000) Principles of behavioral and cognitive neurology, 2nd edn. Oxford University Press, New York

Monk TH (2005) Aging human circadian rhythms: conventional wisdom may not always be right. J Biol Rhythms 20:366–374
Munch M, Knoblauch V, Blatter K, Schroder C, Schnitzler C et al (2004) The frontal predominance in human EEG delta activity after sleep loss decreases with age. Eur J Neurosci 20:1402–1410
Nagy H, Keri S, Myers CE, Benedek G, Shohamy D, Gluck MA (2007) Cognitive sequence learning in Parkinson's disease and amnestic mild cognitive impairment: dissociation between sequential and non-sequential learning of associations. Neuropsychologia 45:1386–1392
Naidoo N (2009) Cellular stress/the unfolded protein response: relevance to sleep and sleep disorders. Sleep Med Rev 13:195–204
Naismith SL, Rogers NL, Hickie IB, Mackenzie J, Norrie LM, Lewis SJ (2010) Sleep well, think well: sleep-wake disturbance in mild cognitive impairment. J Geriatr Psychiatry Neurol 23:123–130
Neikrug AB, Ancoli-Israel S (2010) Sleep disorders in the older adult—a mini-review. Gerontology 56:181–189
Nicolas A, Petit D, Rompre S, Montplaisir J (2001) Sleep spindle characteristics in healthy subjects of different age groups. Clin Neurophysiol 112:521–527
Nissen MJ, Bullemer P (1987) Attentional requirements of learning: Evidence from performance measures. Cognit Psychol 19:1–32
Nissen C, Kloepfer C, Feige B, Piosczyk H, Spiegelhalder K, Voderholzer U, Riemann D (2010) Sleep-related memory consolidation in primary insomnia. J Sleep Res
O'Donnell D, Silva EJ, Munch M, Ronda JM, Wang W, Duffy JF (2009) Comparison of subjective and objective assessments of sleep in healthy older subjects without sleep complaints. J Sleep Res 18:254–263
Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27:1255–1273
Pace-Schott EF, Hobson JA (2002) The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev 3:591–605
Pace-Schott EF, Spencer RM (2011) Age-related changes in the cognitive function of sleep. Prog Brain Res 191:75–89
Pace-Schott EF, Spencer RM (2013) Age-related changes in consolidation of perceptual and muscle-based learning of motor skills. Front Aging Neurosci 5:83
Peters KR, Ray L, Smith V, Smith C (2008a) Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. J Sleep Res 17:23–33
Peters KR, Ray L, Smith V, Smith C (2008b) Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. J Sleep Res 17:23–33
Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183–194
Petersen RC (2011) Clinical practice. Mild cognitive impairment. N Engl J Med 364(23): 2227–2234
Petersen RC, Negash S (2008) Mild cognitive impairment: an overview. CNS Spectr 13:45–53
Petit D, Gagnon JF, Fantini ML, Ferini-Strambi L, Montplaisir J (2004) Sleep and quantitative EEG in neurodegenerative disorders. J Psychosom Res 56:487–496
Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9:534–547
Plihal W, Born J (1999) Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 36:571–582
Potvin O, Lorrain D, Forget H, Dube M, Grenier S et al (2012) Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. Sleep 35:491–499
Puetz J, Grohmann S, Metternich B, Kloepfer C, Feige B et al (2011) Impaired memory consolidation during sleep in patients with functional memory disorder. Biol Psychol 86:31–38
Rabin LA, Pare N, Saykin AJ, Brown MJ, Wishart HA et al (2009) Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. Neuropsychol Dev Cogn 16:357–376

Raggi A, Ferri R (2010) Sleep disorders in neurodegenerative diseases. Eur J Neurol 17: 1326–1338
Rami L, Molinuevo JL, Sanchez-Valle R, Bosch B, Villar A (2007) Screening for amnestic mild cognitive impairment and early Alzheimer's disease with M@T (memory alteration test) in the primary care population. Int J Geriatr Psychiatry 22:294–304
Rasch B, Buchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315:1426–1429
Rasch B, Pommer J, Diekelmann S, Born J (2009) Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci 12:396–397
Rauchs G, Schabus M, Parapatics S, Bertran F, Clochon P et al (2008) Is there a link between sleep changes and memory in Alzheimer's disease? NeuroReport 19:1159–1162
Rektorova I (2011) Mild cognitive impairment exists in Parkinson's disease. J Neural Transm 118:1179–1183
Robertson EM (2009) From creation to consolidation: a novel framework for memory processing. PLoS Biol 7:e19
Robertson EM, Pascual-Leone A, Press DZ (2004) Awareness modifies the skill-learning benefits of sleep. Curr Biol 14:208–212
Salthouse TA (2009) When does age-related cognitive decline begin? Neurobiol Aging 30:507–514
Salthouse TA (2010) Selective review of cognitive aging. J Int Neuropsychol Soc 16(3):1–7
Salzarulo P, Fagioli I, Lombardo P, Gori S, Gneri C et al (1999) Sleep stages preceding spontaneous awakenings in the elderly. Sleep Res Online 2:73–77
Schredl M, Hornung O, Regen F, Albrecht N, Danker-Hopfe H, Heuser I (2006) The effect of donepezil on sleep in elderly, healthy persons: a double-blind placebo-controlled study. Pharmacopsychiatry 39:205–208
Schredl M, Weber B, Leins ML, Heuser I (2001) Donepezil-induced REM sleep augmentation enhances memory performance in elderly, healthy persons. Exp Gerontol 36:353–361
Scullin MK (2013) Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. Psychol Aging 28(1):105–114
Seeck-Hirschner M, Baier PC, Weinhold SL, Dittmar M, Heiermann S et al (2012) Declarative memory performance is associated with the number of sleep spindles in elderly women. Am J Geriatr Psychiatry 20(9):782–788
Siengsukon C, Boyd LA (2009) Sleep enhances off-line spatial and temporal motor learning after stroke. Neurorehabilitation Neural Repair 23:327–335
Siengsukon CF, Boyd LA (2008) Sleep enhances implicit motor skill learning in individuals poststroke. Top stroke Rehabil 15:1–12
Silva D, Guerreiro M, Maroco J, Santana I, Rodrigues A et al (2012) Comparison of four verbal memory tests for the diagnosis and predictive value of mild cognitive impairment. Dement Geriatr Cogn Disord Extra 2:120–131
Simon SS, Yokomizo JE, Bottino CM (2012) Cognitive intervention in amnestic mild cognitive impairment: A systematic review. Neurosci Biobehav Rev 36(4):1163–1178
Skene DJ, Swaab DF (2003) Melatonin rhythmicity: effect of age and Alzheimer's disease. Exp Gerontol 38:199–206
Spencer RM, Gouw AM, Ivry RB (2007) Age-related decline of sleep-dependent consolidation. Learn Mem 14:480–484
Spencer RM, Sunm M, Ivry RB (2006) Sleep-dependent consolidation of contextual learning. Curr Biol 16:1001–1005
Spira AP, Gamaldo AA, An Y, Wu MN, Simonsick EM et al (2013) Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. JAMA Neurol 70:1537–1543
Spreng RN, Wojtowicz M, Grady CL (2010) Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. Neurosci Biobehav Rev 34:1178–1194

Stavitsky K, Neargarder S, Bogdanova Y, McNamara P, Cronin-Golomb A (2012) The impact of sleep quality on cognitive functioning in Parkinson's disease. J Int Neuropsychol Soc 18:108–117

Stickgold R (2005) Sleep-dependent memory consolidation. Nature 437:1272–1278

Terry AV Jr, Buccafusco JJ (2003) The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 306:821–827

Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W (2006) A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem 86:241–247

Tucker M, McKinley S, Stickgold R (2011) Sleep optimizes motor skill in older adults. J Am Geriatr Soc 59(4):603–609

Van Someren EJ, Riemersma RF, Swaab DF (2002) Functional plasticity of the circadian timing system in old age: light exposure. Prog Brain Res 138:205–231

Venneri A, Gorgoglione G, Toraci C, Nocetti L, Panzetti P, Nichelli P (2011) Combining neuropsychological and structural neuroimaging indicators of conversion to Alzheimer's disease in amnestic mild cognitive impairment. Curr Alzheimer Res 8(7):789–797

Walker MP (2009) The role of sleep in cognition and emotion. Ann N Y Acad Sci 1156:168–197

Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211

Wang B, Guo Q, Zhao Q, Hong Z (2012) Memory deficits for non-amnestic mild cognitive impairment. J neuropsychol

Wauquier A (1993) Aging and changes in phasic events during sleep. Physiol Behav 54:803–806

Wei HG, Riel E, Czeisler CA, Dijk DJ (1999) Attenuated amplitude of circadian and sleep-dependent modulation of electroencephalographic sleep spindle characteristics in elderly human subjects. Neurosci Lett 260:29–32

Westerberg CE, Lundgren EM, Florczak SM, Mesulam MM, Weintraub S et al (2010) Sleep influences the severity of memory disruption in amnestic mild cognitive impairment: results from sleep self-assessment and continuous activity monitoring. Alzheimer Dis Assoc, Disord

Westerberg CE, Mander BA, Florczak SM, Weintraub S, Mesulam MM et al (2012) Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. J Int Neuropsychol Soc 3:1–11

Wilson JK, Baran B, Pace-Schott EF, Ivry RB, Spencer RM (2012) Sleep modulates word-pair learning but not motor sequence learning in healthy older adults. Neurobiol Aging 33(5):991–1000

Wong JC, Li Y, Schwarzschild MA, Ascherio A, Gao X (2014) Restless legs syndrome: an early clinical feature of Parkinson disease in men. Sleep 37:369–372

Wulff K, Gatti S, Wettstein JG, Foster RG (2010) Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev 11:589–599

Xie L, Kang H, Xu Q, Chen MJ, Liao Y et al (2013) Sleep drives metabolite clearance from the adult brain. Science 342:373–377

Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP et al (2011) Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 306:613–619

Adenosine, Caffeine, and Performance: From Cognitive Neuroscience of Sleep to Sleep Pharmacogenetics

Emily Urry and Hans-Peter Landolt

Abstract An intricate interplay between circadian and sleep–wake homeostatic processes regulate cognitive performance on specific tasks, and individual differences in circadian preference and sleep pressure may contribute to individual differences in distinct neurocognitive functions. Attentional performance appears to be particularly sensitive to time of day modulations and the effects of sleep deprivation. Consistent with the notion that the neuromodulator, adenosine, plays an important role in regulating sleep pressure, pharmacologic and genetic data in animals and humans demonstrate that differences in adenosinergic tone affect sleepiness, arousal and vigilant attention in rested and sleep-deprived states. Caffeine—the most often consumed stimulant in the world—blocks adenosine receptors and normally attenuates the consequences of sleep deprivation on arousal, vigilance, and attention. Nevertheless, caffeine cannot substitute for sleep, and is virtually ineffective in mitigating the impact of severe sleep loss on higher-order cognitive functions. Thus, the available evidence suggests that adenosinergic mechanisms, in particular adenosine A_{2A} receptor-mediated signal transduction, contribute to waking-induced impairments of attentional processes, whereas additional mechanisms must be involved in higher-order cognitive consequences of sleep deprivation. Future investigations should further clarify the exact types of

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cognitive processes affected by inappropriate sleep. This research will aid in the quest to better understand the role of different brain systems (e.g., adenosine and adenosine receptors) in regulating sleep, and sleep-related subjective state, and cognitive processes. Furthermore, it will provide more detail on the underlying mechanisms of the detrimental effects of extended wakefulness, as well as lead to the development of effective, evidence-based countermeasures against the health consequences of circadian misalignment and chronic sleep restriction.

Keywords Circadian · Homeostasis · Sleep deprivation · Sleepiness · Arousal · Attention · Cognition · ADA · ADORA2A · Plasticity

Contents

1 Circadian and Homeostatic Influences Permit Consolidated Periods of Wakefulness and Sleep

Wakefulness and sleep take place periodically, at specific times, during the 24h light–dark cycle. These two distinct states result from the interplay between circadian and homeostatic oscillators, a concept originally described by the two-process model of sleep–wake regulation (Borbély 1982). The circadian process reflects an endogenous, 24-h variation in the propensity for sleep and wakefulness (Borbély 1982). This latter process is controlled by the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, an anatomical structure considered to be the circadian master clock in mammals. Human research, conducted under a range of experimental conditions (e.g., internal desynchronization of the sleep–wake cycle, forced desynchrony paradigms, fragmented sleep–wake cycles, sleep deprivation, and sleep displacement), has highlighted the existence of a robust drive to maintain wakefulness toward the end of the habitual waking day (Lavie 2001). Thus, the circadian master clock promotes wakefulness in the early evening, just before habitual time for sleep. The positioning of this "wake maintenance zone" (Strogatz et al. 1987), at the end of the waking day, may seem paradoxical. However, it is thought that this high circadian-based tendency for wakefulness is what prevents humans from falling asleep during the early evening, when homeostatic sleep pressure reaches its highest level. The homeostatic process represents an hourglass mechanism, which gradually builds up with increasing time awake, and roughly exponentially declines during sleep. Thus, circadian and homeostatic systems work in opposition to ensure a consolidated period of wakefulness (Cajochen et al. 2010). Opposite effects of the two processes also occur as the biological night progresses and allows the maintenance of a consolidated sleep episode (Dijk and Czeisler 1994, 1995). The SCN may promote a circadian increase in sleep tendency, which counteracts the decrease in homeostatic sleep propensity as the individual accumulates sleep.

2 The Endogenous Circadian Clock Modulates Cognitive Performance

The states of subjective sleepiness and alertness, as well as distinct neurobehavioral functions (e.g., cognitive performance on specific tasks), are also influenced by this interplay between circadian and homeostatic processes (reviewed by

Cajochen et al. 2004). Indeed, from a cognitive perspective, the two-process model of sleep–wake regulation implies that neurobehavioral efficiency may change over the day due to the influence of circadian timing on alertness and task performance, due to increasing homeostatic sleep pressure, or due to a combination of both these factors (Carrier and Monk 2000). For example, research incorporating a 40-h constant routine protocol revealed a clear circadian modulation of subjective sleepiness (Karolinska Sleepiness Scale) (Gillberg et al. 1994) and cognitive performance (psychomotor vigilance task [PVT]) (Dinges and Powell 1985), even in the absence of strong homeostatic sleep pressure (Cajochen et al. 2001; Graw et al. 2004). This protocol permits the manipulation of homeostatic sleep pressure by either sleep depriving (high sleep pressure) or sleep satiating (low sleep pressure) study participants by the allowance of regular nap opportunities throughout the circadian cycle. This circadian modulation of subjective state and neurobehavioral performance is organized in a temporal manner which prompts maximal performance throughout the waking hours, including the wake-maintenance zone. Yet, if testing continues into the biological night (e.g., under sleep deprivation conditions), there is a significant decline in performance, which coincides with the decline of the circadian arousal signal. Importantly, however, performance deterioration moves in line with the circadian cycle, such that an improvement can be observed in the biological morning, once the circadian drive for wakefulness takes center stage once again (Cajochen et al. 2004).

2.1 Individual Differences in Circadian Preference Modulate Human Neurobehavioral Performance

Forced desynchrony paradigms can be used to separate the influence of the circadian pacemaker from the influence of homeostatic sleep pressure. Here, subjects are isolated from the usual "zeitgebers" (i.e., time givers such as light) and for weeks are exposed to an artificial sleep/wake schedule with a "day" duration that is significantly shorter (e.g., 19 h) or longer (e.g., 28 h) than the normal 24-h day. With time, the protocol forces a progressive desynchronization of the artificial sleep–wake cycle from the endogenous circadian cycle. Such research indicates that the extent to which circadian rhythm modulates performance is largely dependent on the extent of homeostatic sleep pressure. Specifically, rising sleep pressure attenuates circadian arousal during the subjective evening hours (Dijk and Archer 2009). As a result, even small changes in the relationship between the two processes may have an important effect on an individual's ability to maintain a consistent cognitive performance during the normal waking day (Cajochen et al. 2010). In fact, as reviewed by Schmidt and colleagues (2007), large differences in circadian parameters can be observed in the temporal disposition of an individual, and this gives rise to differential modulations in cognitive performance across the normal waking day. Prominent inter-individual variation in circadian preference significantly affects the temporal organization of a wealth of human behaviors.

Morningness–eveningness is the most substantial source of this variation (Roenneberg et al. 2003), and is expressed by favorite periods for diurnal activities, such as working hours, and specific sleep habits (Taillard et al. 2003). Such behaviors in turn reflect the particular chronotype of the individual. The morningness–eveningness chronotype can be assessed using self-report questionnaires, such as the morningness–eveningness questionnaire (Horne and Östberg 1976) and the Munich Chronotype Questionnaire (Roenneberg et al. 2003). At one end of the scale exist extreme morning types, who show a strong preference for waking up early in the morning and find it difficult to remain awake beyond their usual bedtime. At the opposite end of the scale, extreme evening types prefer to go to bed late at night, and experience great difficulty in getting up in the morning (Schmidt et al. 2007). It has been suggested that these extreme chronotypes are "phase shifted" according to their circadian rhythmicity. That is, their peaks and troughs of physiological circadian markers (core body temperature, melatonin) occur either earlier (phase advance, morning types) or later (phase delay, evening types) in relation to the external clock time, as compared to "neutral" individuals who show no strong preference for morningness or eveningness (Duffy et al. 2001). Importantly, as well as differences in physiological characteristics, the diurnal profile of some neurobehavioral variables is also influenced by chronotype. Accordingly, alertness and performance may peak at different clock times, depending on the chronotype of the individual. For example, some people may be consistently at their best in the morning, while others are more alert and perform better in the evening (Schmidt et al. 2007).

To sum up, subjective sleepiness and alertness, and neurobehavioral performance, are contingent upon the synchronicity between the individual's peak periods of circadian arousal and the time of day at which testing takes place (Schmidt et al. 2007). Accordingly, it could be intuitively assumed that individuals who feel subjectively sleepier and less alert, are more likely to be cognitively impaired (Leproult et al. 2003). However, there is accumulating evidence to contradict this proposal. For example, sleep deprivation protocols have revealed that subjective sleepiness and objective alertness are not always linked to measures of neurobehavioral performance (Leproult et al. 2003). In fact, subjective measures of alertness and performance can differ to a great extent (Van Dongen et al. 2003). Such findings raise the question as to whether different cognitive domains are differentially affected by circadian rhythms, reflected by testing subjects at different times of the day.

2.2 Circadian Influences Differently Affect Distinct Cognitive Performance Tasks

Cognitive functioning domains range from simple attention to logical reasoning, working memory, long-term memory, and more complex executive functions. A simplified overview and classification of the main cognitive processes (attention,

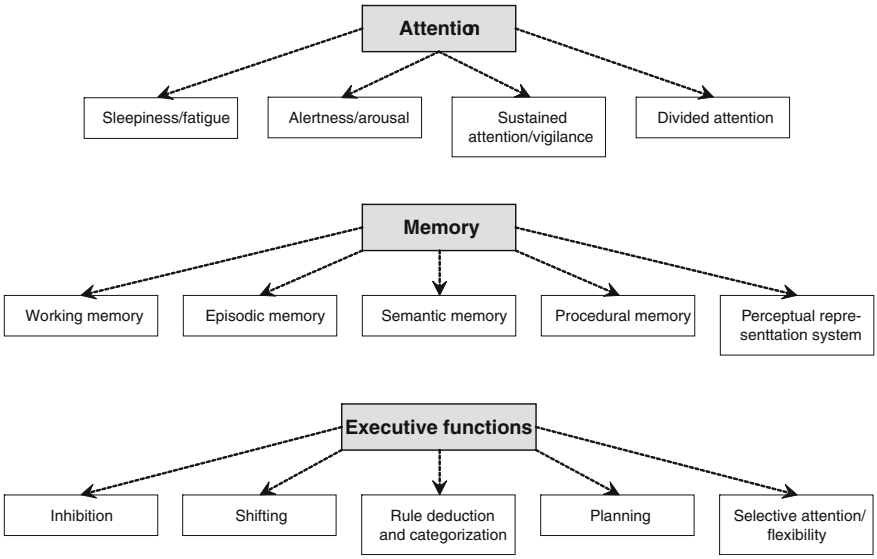

Fig. 1 Overview and simplified global classification of the main cognitive processes. See (Schmidt et al. 2007) for more detailed explanations

memory, and executive functions) can be seen in Fig. 1 (adapted from Schmidt et al. 2007).

Most studies on the circadian modulation of cognitive function have focused on the impact of time of day on vigilance and basic attentional parameters (Schmidt et al. 2007). Historically, research revealed a temporal relationship between circadian variations in cognitive performance measures and daily fluctuations in physiological variables such as core body temperature. That is, when body temperature is high and endogenous melatonin is low, alertness and neurobehavioral performance tend to be higher (Kleitman et al. 1938). It was suggested that the circadian-related increase in body temperature would indirectly speed up cognitive processing by increasing metabolic activity in the brain (Kleitman et al. 1938). However, further research highlighted the role of other, external factors, on time-of-day effects in cognition. More specifically, peak and troughs in performance can be attributed to the type and difficulty of the task (e.g., differential working-memory load) (Folkard et al. 1983). While performance speed on simple repetitive and serial search tasks peaks with temperature levels in the evening (Colquhoun 1981; Monk 1982), speed performance on more complex cognitive tasks (e.g., logical reasoning tasks) peaks in the late morning (Folkard 1975), and performance in short-term memory retention peaks in the early to mid-morning (Laird 1925). Thus, Bonnet proposed that the optimal time of day for completing a cognitive test is largely dependent on the specific parameters of the task, such as its cognitive domain, duration and difficulty, the administration method, and the measured variable (Bonnet 2000). Alternative data, however, revealed that the

selected paradigm (e.g., normal sleep/wake conditions vs. 40 h of enforced wakefulness during constant routine) also influences temporal performance (Cajochen et al. 1999). Moreover, compensatory mechanisms, such as motivational factors and expectancy due to experience, also play a role in the outcome (Schmidt et al. 2007).

To date, the picture that emerges is that time-of-day modulations affect performance on a range of cognitive tasks, and these performance fluctuations are additionally contingent upon inter-individual differences in circadian preference (i.e., chronotype). It seems that only highly practiced responses (e.g., constant performance tasks) (Valdez et al. 2005) are rather invariant across the day, with all other responses being vulnerable to the time-of-day effect during normal day–night conditions, as they require a certain degree of control over stimuli and responses. Above attentional processes, higher-order cognitive functions, such as working-memory load or executive control, appear to be particularly sensitive to time-of-day modulations (Mikulincer et al. 1989). However, given the current lack of research in this domain, and the varying choices of protocol and experimental control, it is impossible to conclude whether different tasks, involving a range of cognitive processes or differing in difficulty, exhibit genuine differences in time-of-day modulations (Schmidt et al. 2007).

3 Sleep Pressure Modulates Cognitive Performance

3.1 Sleep Deprivation Affects Attentional Processes

According to the "wake state instability" hypothesis (Doran et al. 2001), neurobehavioral performance becomes increasingly variable under the influence of elevated sleep pressure due to inadvertent microsleep episodes, with brief moments of low arousal that make it difficult to sustain attention. This unstable state, which fluctuates from second to second, is characterized by increased lapses of attention, increased numbers of errors in response, but also increased compensatory efforts resulting in normal reaction times for a short period of time. Over the last two decades, the instrument that has emerged as the dominant assay of vigilant attention in paradigms of sleep loss is the PVT (Dinges et al. 1985). This task has been widely used in human studies to detect the sustained attention (or "vigilance") deficits associated with different types of sleep loss, including chronic sleep restriction (Belenky et al. 2003; Van Dongen et al. 2003) and sleep deprivation (Doran et al. 2001; Rétey et al. 2006). Importantly, the task is highly sensitive to sleep loss, independent of aptitude, lacks learning effects, and its reliability and validity have been amply demonstrated (Lim and Dinges 2008). The PVT is a test of simple reaction time to a cue that occurs at random inter-stimulus intervals. During the task (standard duration of 10 min) subjects are instructed to attend to a small, rectangular area on a dark screen. They are then required to

respond as quickly as possible whenever they perceive the appearance of a bright millisecond counter inside this rectangular area. Stopping the counter allows subjects to view their reaction time, which serves as feedback for that particular trial. Button presses, when the counter is not displayed on the screen, are counted as false starts, which subjects are instructed to avoid. Four dominant findings have emerged from the use of the PVT in sleep research protocols. First, sleep deprivation results in an overall slowing of responses. Second, sleep deprivation increases the propensity of individuals to lapse for lengthy periods (>500 ms), as well as make false starts. Third, sleep deprivation enhances the time-on-task effect, the phenomenon whereby performance worsens across the course of a cognitive task owing to fatigue and reduced motivation. Finally, PVT results during extended periods of wakefulness reveal the presence of interacting circadian and homeostatic sleep-regulatory processes (Lim and Dinges 2008).

3.2 Sleep Deprivation Affects Higher-Order Cognitive Processes

Sleep deprivation has been shown to have significant adverse effects on a range of higher-order cognitive processes, including memory encoding, consolidation, and retrieval (Walker 2008), behavioral inhibition (Drummond et al. 2006; Harrison et al. 2007), judgment (Killgore et al. 2007a), planning (Horne 1988; Killgore et al. 2009), and divergent thinking capacities (Horne 1988). All such processes are believed to draw heavily upon resources in the prefrontal cortex (Killgore et al. 2011). Moreover, recent research from rodent experiments has highlighted that sleep deprivation is associated with reduced neural activity within brain regions involved in memory (frontal cortex and hippocampus), emotion (amygdala), and regulation of the sleep–wake cycle (anterior hypothalamus and supraoptic nucleus) (Hagewoud et al. 2011; Pierard et al. 2007; Vecsey et al. 2009). Disruption of any of these distinct facets of cognition by sleep deprivation may contribute to noteworthy errors in decision making (reviewed by Killgore 2010). Interestingly, however, deficits in executive functions have not been observed universally, particularly during shorter durations of sleep deprivation, such as one night (Pace-Schott et al. 2009). This suggests that the brain's executive function systems may temporarily compensate for brief sleep loss by utilizing additional cognitive resources via activation of alternative brain regions (Drummond et al. 2000, 2005b).

More recently, research has focused on clarifying the ways in which sleep deprivation may influence well-characterized, higher cognitive processes, such as mental heuristics and emotional biases that affect risk assessment and decision making (Killgore et al. 2012). For example, McKenna and colleagues (2007) revealed that when the possible outcomes from a gambling task were framed in terms of potential gains, sleep deprivation prompted subjects to take more risks compared to when they were well rested. Yet, when the same task was presented in

terms of potential losses, lack of sleep led them to take fewer risks than usual. Such findings indicate that sleep deprivation may lead to greater reliance upon preexisting cognitive biases. Moreover, functional neuro-imaging studies have highlighted that sleep-deprived individuals show differences within brain-reward circuitry during risky decision making, and this may bias them toward expectations of gains while reducing their focus on losses (Venkatraman et al. 2007).

Another way that prolonged wakefulness affects decision making is by reducing the weight that a person places on new information when making choices (Dickinson and Drummond 2008). Sleep deprived individuals may tend to rely more upon automatic, as opposed to effortful, forms of cognitive processing (Killgore et al. 2012). Emotional biasing is a form of automatic processing that may influence decision making. Indeed, Damasio (1994) proposed that emotional reactions act as a cognitive streamlining function that quickly and efficiently narrows an individual's choice of options. These emotional "gut reactions" prime a person to make choices based on how rewarding or unpleasant they found a previous similar experience. In an experimental setting, this emotion-guided decision making can be investigated using the Iowa Gambling Task (IGT) (Bechara et al. 1994). During the computerized program, participants are presented with four decks of cards placed face down. Next, players are required to select 100 cards from these four available packs. On card selection, they are immediately informed as to whether the card they selected results in a monetary gain or a monetary loss. Unbeknownst to the subject, however, two of the decks are "good" decks and lead to small but consistent net gains; while the other two decks are "bad" decks, and comprise large short-term gains but consistent long-term losses. With regard to the results, healthy individuals usually learn from the trial-by-trial feedback and adjust their playing strategy to avoid the risky bad decks in favor of the modest, but consistently advantageous, good decks (Bechara 2004). However, patients with damage to the ventromedial prefrontal cortex (vmPFC) fail to make this adjustment (Bechara 2004). Such findings are in line with evidence that damage to the vmPFC leads to shortsightedness for the future (Bechara et al. 1994), as well as neuroimaging data that indicates that this brain region plays a key role in the decision making process of the IGT (Li et al. 2010).

Importantly, the vmPFC seems to be particularly affected by sleep deprivation. Metabolic activity in this brain region is drastically reduced after a single night of sleep loss (Thomas et al. 2000), whereas increased activation of this area is correlated to a subject's degree of responsiveness to rewards during sleep-deprived decision making (Venkatraman et al. 2011). Accordingly, in a series of studies performed by Killgore and colleagues (2006, 2007b), the IGT was used to assess the effects of sleep deprivation on emotionally-guided decision making. As predicted, well-rested subjects rapidly learned the contingencies of the task. However, following 49 (Killgore et al. 2006) and 75 h (Killgore et al. 2007b) of prolonged wakefulness, the same participants showed a significant decline in decision making performance. Specifically, they became progressively more risk-taking and shortsighted in decision making, tending to prefer risky short-term gains at the expense of incurring long-term losses. Overall, such findings indicate that prolonged sleep

loss is associated with making choices that begin to favor short-term over long-term outcomes—a pattern paralleling that often observed among patients with lesions to the vmPFC (Bechara 2004). Since the vmPFC is important in several key cognitive-affective processes (Damasio 1994), alterations in vmPFC functioning, or its associated neuro-circuitry following sleep loss, may indeed underlie some of the subtle changes in decision making observed in the two Killgore et al. studies. The findings are also in accordance with evidence suggesting that sleep deprivation leads to difficulty incorporating new information into ongoing decision making processes, implying an overall decline in cognitive flexibility, in favor of greater reliance on automatic cognitive processes (Dickinson and Drummond 2008).

Taken together, these behavioral findings suggest that distinct higher-order cognitive processes are impaired by sleep deprivation. The sensitivity of the prefrontal cortex to the effects of sleep loss may also be reflected in distinct neurophysiological changes associated with sleep deprivation. For example, regional cerebral blood flow in this region correlates with electroencephalogram (EEG) slow-wave activity (SWA; power density in the 0.75–4.5 Hz range) in non-rapid-eye-movement (NREM) sleep (Dang-Vu et al. 2010), which represents the primary physiological marker of sleep homeostasis (Achermann and Borbély 2011). Moreover, not only the increase in SWA in NREM sleep, but also the rise in EEG theta ($\sim$5–9 Hz range) activity after prolonged wakefulness (Cajochen et al. 1995) is larger over anterior than over posterior cortical areas (Finelli et al. 2000).

4 Cerebral Underpinnings of Circadian and Homeostatic Influences on Performance

Accumulating evidence demonstrates that circadian and homeostatic sleep–wake regulatory processes interact in a fine-tuned manner to modulate cognitive performance (Schmidt et al. 2012). Neural connections from the SCN indirectly reach target areas implicated in sleep homeostasis, including ventro-lateral-preoptic area, tuberomammillary nucleus, lateral hypothalamus, thalamus, and brainstem nuclei via its connections to the dorsal medial hypothalamus (Mistlberger 2005). Simultaneously, diffuse monoaminergic activating systems are under circadian control and adjoin with many thalamo-cortical areas, which suggests that the interaction with sleep homeostasis takes place at many different levels (Dijk and Archer 2009).

Research conducted by Aston-Jones and colleagues indicated that the noradrenergic locus coeruleus plays an important role in the circadian regulation of arousal (2001, 2005). Activity in the locus coeruleus, combined with its widespread thalamic and cortical connections, may modulate a variety of central nervous system functions, including alertness and vigilance, and also higher-order cognitive processes (Cajochen et al. 2010). Moreover, a recent study incorporating behavioral assessments, EEG, and functional magnetic resonance imaging (fMRI) in morning

and evening chronotypes indicated that homeostatic sleep pressure exerts an influence on attention-related cerebral activity in key structures crucially involved in generating the circadian wake-promoting signal, including the locus coeruleus. Specifically, maintenance of optimal attentional performance in the evening after a normal waking day was associated with higher activity in evening chronotypes than in morning chronotypes in locus coeruleus and anterior hypothalamus, including the SCN (Schmidt et al. 2009). Furthermore, activity in the anterior hypothalamus decreased with increasing homeostatic sleep pressure, as indexed by EEG SWA in the first NREM sleep episode. These data suggest that circadian and homeostatic interactions contribute to the neural activity that underlies diurnal variations in human behavior. Interestingly, the differential activation pattern was observed only for optimal performance on the PVT (i.e., the fastest 10th percentile of reaction times) (Schmidt et al. 2012), which reflects the phasic ability to recruit the attentional network above normal levels (Drummond et al. 2005a).

The mechanisms by which circadian oscillations in the SCN, as well as circuits controlling for states of wakefulness and sleep, interact at the cerebral level in order to regulate arousal and cognitive behavior, are yet to be clarified (Cajochen et al. 2010). Conceptually, endogenous "sleep substances" may accumulate during wakefulness and modify activity in key areas regulating cortical arousal, including brainstem, hypothalamic nuclei and basal forebrain. During sleep, the "sleep substances" would dissipate. Although the biochemical "substrate" of sleep homeostasis remains poorly understood, adenosine, nitric oxide, prostaglandin D_2, tumor necrosis factor alpha, interleukin-1, growth-hormone-releasing hormone, and brain-derived neurotrophic factor are considered to be important candidate mediators of the consequences of prolonged wakefulness (Krueger et al. 2008).

5 A Role for Adenosine in Homeostatic Sleep–Wake Regulation

Compelling and converging evidence in animals and humans has accumulated over the past two decades to support a role for adenosine and adenosine receptors in sleep–wake regulation (see A et al. 2008; Landolt 2008; Porkka-Heiskanen and Kalinchuk 2011 for reviews). Animal studies suggest that the extracellular adenosine concentration in the brain may increase during prolonged wakefulness and decline during (recovery) sleep (Porkka-Heiskanen et al. 2000).

5.1 Adenosine Formation, Transport, and Metabolism

The formation of adenosine in the brain changes in an activity-dependent manner and different mechanisms contribute to the appearance of adenosine in extracellular space. Increased energy demand during wakefulness leads to the break-down

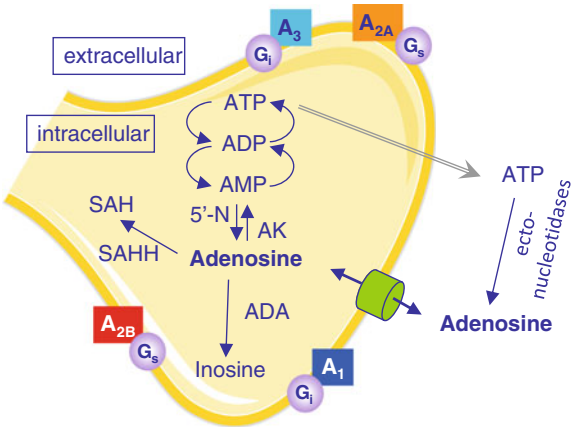

Fig. 2 Schematic representation of adenosine formation, metabolism, and transport. Neurons, astrocytes and microglia cells can release adenosine and adenosine-tri-phosphate (ATP; *gray arrow*). All cell types express adenosine receptors, adenosine transporters (*cylinder*), and ecto-nucleotidases that convert ATP into adenosine. A_1, A_{2A}, A_{2B}, A_3: adenosine receptors coupled to corresponding *G*-proteins; *ADP*: adenosine-di-phosphate; *AMP*: adenosine-mono-phosphate; *SAH*: *S*-adenosyl-homo-cysteine; 5′-*N*: 5′-nucleotidase; *AK*: adenosine kinase; *ADA*: adenosine deaminase; *SAHH*: *S*-adenosyl-homocysteine hydrolase

of energy-rich adenine nucleosides such as adenosine-tri-phosphate (ATP). Adenosine is formed in neurons by 5′-nucleotidase and transported through plasma and intracellular membranes by specialized transporters, including sodium-driven concentrative, and equilibrative nucleoside transporters (Fig. 2). The concentrative transporters use energy to move adenosine into the cell, whereas the equilibrative transporters transport adenosine according to the extracellular/intracellular concentration gradient. Elevated intracellular adenosine concentrations following increased utilization of ATP in conditions of high energy demand lead to release of adenosine. In addition, extracellular adenosine is also formed by ecto-nucleotidases through hydrolysis of ATP. Release of ATP from synaptic vesicles occurs along with several other neurotransmitters, including the major excitatory neurotransmitter glutamate (Haydon and Carmignoto 2006). Finally, ATP and glutamate are also released from astrocytes by a recently established process referred to as gliotransmission. Molecular genetic manipulations in mice strongly suggest that glial cells provide a significant source of extracellular adenosine in the brain (Haydon and Carmignoto 2006). Furthermore, astrocyte-derived ATP may activate purinergic (e.g., $P2X_7$) receptors and affect sleep independently from adenosine (Krueger et al. 2008, 2010).

Clearance of extracellular adenosine mostly occurs through the non-concentrative nucleoside transporters (Fredholm et al. 2005). The main intracellular metabolic pathways of adenosine are the formation of adenosine-monophosphate by adenosine kinase, and the irreversible breakdown to inosine by adenosine deaminase (ADA). Ecto-ADA also catalyzes the extracellular deamination of

adenosine. Mainly due to the high activity of adenosine kinase, baseline levels of extracellular adenosine usually remain low. The action of ADA, which appears to be more abundantly expressed in astrocytes than in neurons (Fredholm et al. 2005), may be particularly important when elevated concentrations of adenosine have to be cleared, such as after sleep deprivation. Both, molecular genetic manipulations of adenosine kinase in mice (Palchykova et al. 2010), as well as genetically reduced ADA enzymatic activity in humans (Rétey et al. 2005), increase deep slow wave sleep and EEG SWA in NREM sleep. These findings provide strong additional support to the idea that adenosine importantly contributes to the homeostatic control of sleep.

5.2 *Adenosine Affects Neuronal Systems Regulating Wakefulness and Sleep*

Adenosine attenuates the activity of wakefulness/vigilance-promoting neurons in brainstem (e.g., locus coeruleus), basal forebrain (BF), and hypothalamus (e.g., tuberomammillary nucleus) and may contribute to cortical disfacilitation, a form of inhibition due to reduced activating input from ascending cholinergic and monoaminergic pathways. As suggested by intracellular recordings in non-anaesthetized cats the long-lasting hyperpolarizing potentials in NREM sleep, which provide the cellular substrate of EEG SWA, may represent periods of disfacilitation (Steriade et al. 2001; Timofeev et al. 2001). Moreover, adenosine activates neurons of the hypothalamic ventro-lateral-preoptic area by reducing inhibitory γ-amino-butyric-acid (GABA)-ergic inputs. These neurons fire significantly faster after sleep deprivation than they do during normal sleep, indicating that their activity is modulated by homeostatic mechanisms representing sleep need (Sherin et al. 1996).

One current hypothesis based upon biochemical, pharmacological, electrophysiological, and behavioral studies postulates that elevated adenosine in the BF plays a distinct role in mediating the sleep deprivation-induced increase in sleepiness and homeostatic sleep drive (Basheer et al. 2004; Porkka-Heiskanen and Kalinchuk 2011; Strecker et al. 2000). It may be important to note, however, that Blanco-Centurion and colleagues highlighted that the actions of adenosine are not restricted to the BF region (2006). This research team used a lesion and pharmacological approach to reveal that adenosine accumulation in the BF is not necessary for sleep induction, and also that BF cholinergic neurons are not essential for sleep drive. Thus, the available data rather suggest that extracellular adenosine provides a global feedback signal on a neuronal network, including subcortical and cortical structures (Franks 2008), that regulates important functional aspects of wakefulness and sleep.

6 Adenosine A_1 and A_{2A} Receptors Mediate Effects of Adenosine in Sleep–Wake Regulation

The cellular effects of adenosine are mediated via four subtypes of G-protein coupled adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 receptors. In vitro studies indicate that physiological concentrations of endogenous adenosine can activate A_1, A_{2A}, as well as A_3 receptors. Nevertheless, it is widely accepted that the high-affinity A_1 and A_{2A} receptors are primarily involved in mediating the effects of adenosine on sleep and vigilance, at least in humans (Sebastiao and Ribeiro 2009).

6.1 Adenosine A_1 Receptors and the Effects of Prolonged Wakefulness

The stimulation of A_1 receptors opens several types of K^+-channels, inhibits adenylate cyclase through activation of G_i proteins and inactivates transient voltage-dependent Ca^{2+}-channels. The A_1 receptor is ubiquitously, but not homogenously, expressed in the central nervous system (Bauer and Ishiwata 2009). In vivo PET with the selective A_1 receptor antagonist, ^{18}F-CPFPX, revealed highest receptor occupancy in striatum and thalamus, as well as temporo-parietal and occipital cortex (Fig. 3a). Pre- and post-synaptic activation of A_1 receptors inhibits excitatory neurotransmission. This receptor subtype, therefore, has long been assumed to play an important role in sleep–wake regulation. Pharmacologic and genetic studies in rats and mice, as well as molecular imaging in humans, partly support this notion. For example, inducible knock-out of neuronal A_1 receptors in mice reduces SWA (3.0–4.5 Hz range) in NREM sleep under baseline conditions, and attenuates the homeostatically regulated rise in SWA after sleep restriction (Bjorness et al. 2009). Moreover, prolonged wakefulness appears to up-regulate A_1 receptor binding in subcortical and cortical brain structures in animals and humans (Elmenhorst et al. 2007, 2009). Taken together, these data indicate a role for adenosine A_1 receptors in mediating distinct consequences of sleep deprivation.

6.2 Adenosine A_{2A} Receptors and the Effects of Prolonged Wakefulness

The stimulation of A_{2A} receptors increases adenylate cyclase activity through activation of G_s (or G_{olf} in striatum) proteins, induces the formation of inositol phosphates, and activates protein kinase A. Compared to the A_1 receptor, this adenosine receptor subtype is less widely distributed in the brain (Bauer and Ishiwata 2009). The highest expression in the human central nervous system is found in basal ganglia (particularly in putamen and caudate nucleus) (Fig. 3b).

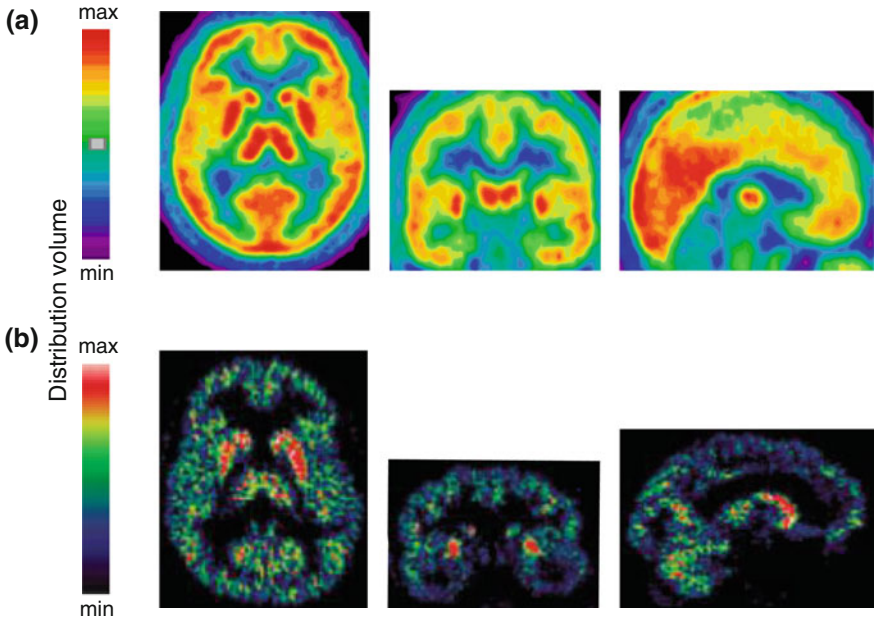

Fig. 3 Distribution of adenosine A_1 and A_{2A} receptors in the human brain. **a** Color-coded distribution volumes of the selective A_1 receptor antagonist, ^{18}C-CPFPX (mean values of 10 healthy young men). From *left* to *right*: axial, coronal, and sagittal planes (coordinates according to the Montreal Neurological Institute brain atlas: $z = -4$, $y = -12$, $x = 0$) (Unpublished data). **b** Color-coded distribution volumes of the selective A_{2A} receptor antagonist, ^{11}C-KW6002 (istradefylline), in a healthy male volunteer. From *left* to *right*: axial, coronal, and sagittal sections. Figure modified from (Brooks et al. 2008)

Recent studies in rodents, including experiments in knock-out mice, suggest that also A_{2A} receptors contribute to the effects of adenosine on sleep. Local administration of the selective A_{2A} receptor agonist, CGS21680, to the subarachnoid space adjacent to BF and lateral preoptic area increases *c-fos* expression in the ventro-lateral-preoptic area and promotes NREM sleep (Scammell et al. 2001). Direct activation of sleep-promoting neurons of the ventro-lateral-preoptic region upon stimulation of A_{2A} receptors could underlie this effect (Gallopin et al. 2005). Interestingly, preliminary data suggested that mice with A_{2A} receptor loss-of-function have reduced sleep and an attenuated sleep rebound after sleep deprivation (Hayaishi et al. 2004), indicating that A_{2A} receptors are part of the neural network that regulates sleep homeostasis in mammals. These findings are supported by recent data in humans, suggesting that genetic variants of the A_{2A} receptor gene (*ADORA2A*) modulate the sleep deprivation-induced increase in EEG SWA in NREM sleep (Bodenmann et al. 2012; Landolt 2012).

In conclusion, both adenosine A_1 and A_{2A} receptor subtypes probably mediate functional effects of adenosine after sleep deprivation, whereas distinct effects may be site- and receptor-dependent.

7 Adenosine and Sleep-Associated Cognitive Functions

7.1 Sleep Deprivation, Adenosine, and Vigilant Attention

While a wealth of evidence supports the concept that modulation of cerebral adenosine contributes to the regulation of wakefulness and sleep, it was not until more recently that research revealed how this manipulation could also alter neurobehavioral performance (Christie et al. 2008). This is poignant given that the BF in particular has been implicated not only in adenosinergic mechanisms of sleep regulation but also in the control of sustained attention (Baxter and Chiba 1999). Thus, the fact that decrements in sustained attention tend to occur concomitantly with feelings of sleepiness, is consistent with studies indicating that the same mechanisms implicated in the control of the homeostatic sleep drive, are also involved in the regulation of attention (Zaborszky et al. 1997). Moreover, neurons within the BF project to components of the cortical sustained attention network, whose activation is linked with optimal human performance on the PVT (Drummond et al. 2005a). More recently, a rat version of the PVT was developed that enabled invasive investigations of the role of adenosine and the BF in the control of behavioral state and sustained attention (Christie et al. 2008). Christie and colleagues (2008) utilized this task to assess the effects of elevated cerebral adenosine on vigilant performance. The study revealed that rats receiving infusions of adenosine in the BF immediately prior to performing the PVT showed prolonged response latencies and more performance lapses. The effect was blocked by the co-administration of the A_1 receptor antagonist, 8-cyclopentyl-theophylline, demonstrating that the performance decrements were indeed due to elevated adenosine in the BF and apparently mediated by A_1 receptors, as opposed to other, unrelated factors (Christie et al. 2008). Furthermore, the adenosine-induced impairments in sustained attention were similar to those seen in rats undergoing sleep deprivation (Cordova et al. 2006). These findings are consistent with the hypothesis that sleep loss induces an accumulation of adenosine in the BF, which leads to increased sleepiness and reduced vigilance.

Local cerebral administration of adenosine is not possible in humans, to study its role in reduced vigilant attention during sleep deprivation. Nevertheless, relevant information has been obtained from studies on a naturally occurring genetic variation of the gene encoding the adenosine metabolising enzyme ADA. A *G*-to-*A* single nucleotide polymorphism at nucleotide 22 of the gene encoding ADA underlies an Asp-to-Asn amino-acid substitution at codon 8 of the ADA protein. Compared to *G*/*G* homozygotes, carriers of the variant allele show reduced ADA activity in vitro (Battistuzzi et al. 1981; Riksen et al. 2008), and presumably elevated tissue adenosine levels in vivo (Hirschhorn et al. 1994). This functional polymorphism not only modulates the duration and intensity of slow wave sleep (Bachmann et al. 2012; Mazzotti et al. 2012; Rétey et al. 2005), but also human attentional performance in rested and sleep-deprived states. More specifically, carriers of the *G*/*A* genotype ($n = 29$) performed worse on the *d*2 focused attention

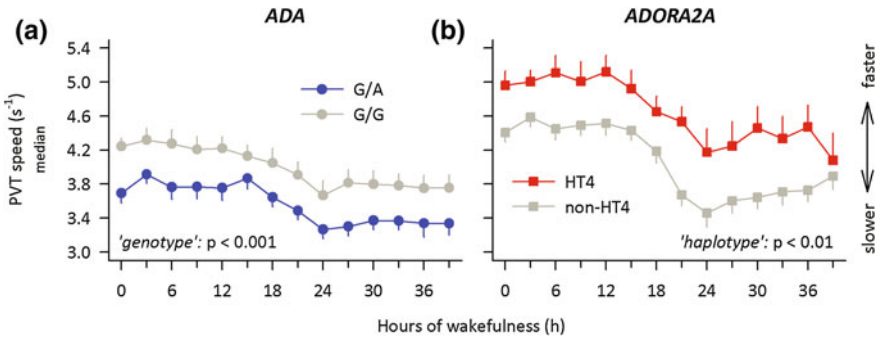

Fig. 4 Functional variants of genes contributing to adenosine metabolism (adenosine deaminase, *ADA*) and signal transmission (adenosine A_{2A} receptor, *ADORA2A*) contribute to inter-individual differences in psychomotor vigilance during prolonged wakefulness. Starting 30 min after wake-up from the baseline night, a 10-min psychomotor vigilance task (PVT) was administered at 3-h intervals during 40 h prolonged wakefulness. Ticks on the *x*-axis are rounded to the nearest hour. The time courses of median speed (1/reaction times) are illustrated; error bars indicate + or − 1 SEM. Data were analyzed with 2-way ANOVA models with the factors *'genotype'* (*G/A*, *G/G*) or *'haplotype'* (HT4, non-HT4) and *'session'* (14 assessments during prolonged waking). **a** *Blue circles*: *G/A* genotype ($n = 11$). *Grey circles*: *G/G* genotype ($n = 11$). The *G/A* genotype of *ADA* performs worse than the G/G genotype throughout prolonged waking (*'genotype'*: $F_{1,\ 25} = 15.4$, $p < 0.001$; *'session'*: $F_{13,\ 239} = 38.6$, $p < 0.001$; *'genotype'* × *'session'* interaction: $F_{13,\ 146} = 0.3$, $p > 0.9$). Data were re-plotted from (Bachmann et al. 2012). **b** *Red squares*: Carriers of HT4 haplotype alleles ($n = 6$). *Gray squares*: Carriers of HT4 haplotype alleles ($n = 17$). See (Bodenmann et al. 2012) for details of genetic analyses. Individuals with haplotype HT4 performed faster than non-HT4 allele carriers throughout sleep deprivation (*'haplotype'*: $F_{1,\ 21} = 9.3$, $p = 0.006$; *'session'*: $F_{13,\ 273} = 16.3$, $p < 0.001$; *'haplotype'* × *'session'* interaction: $F_{13,\ 273} = 0.9$, $p > 0.5$). Data were reanalyzed from (Bodenmann and Landolt 2010)

task than *G/G* homozygotes ($n = 191$) (Bachmann et al. 2012). The difference was also present between two prospectively matched subgroups of *G/A* ($n = 11$) and *G/G* ($n = 11$) genotypes. Moreover, sustained attention (Fig. 4a) and vigor were reduced, whereas waking EEG alpha activity (8.5–12 Hz), sleepiness, fatigue, and *a*-amylase activity in saliva were enhanced in *A*-allele carriers when compared to *G/G* homozygotes. These convergent data demonstrate that genetic reduction of ADA activity in healthy humans not only modulates the quality of sleep, but also the quality of wakefulness, including neurobehavioral performance.

7.2 Sleep Deprivation, Adenosine, and Higher-Order Cognitive Functions

As discussed previously, Bjorness and colleagues (2009) revealed that conditional knock-out of the A_1 receptor elicits selective attenuation of the SWA rebound following restricted sleep. This research team also investigated the effects of this genetic manipulation on working memory. It demonstrated that animals lacking

the A_1 receptor not only showed a reduced rebound SWA response, but they also failed to maintain normal cognitive function, although this function was normal when sleep was not restricted. Since the attenuation of SWA is associated with compromised working memory performance, this indicates a functional role for adenosine A_1 receptor-dependent SWA homeostasis in maintaining this cognitive ability when sleep is restricted (Bjorness et al. 2009). Here, it is worth noting that the loss of the A_1 receptors in the conditional gene deletion used in this study is exclusively neuronal. Nevertheless, the source of the adenosine includes both neuronal and non-neuronal, or glia, cells (Pascual et al. 2005; Studer et al. 2006). Halassa and colleagues (2009) inhibited the release of adenosine from glia cells in transgenic mice expressing a dominant-negative (dn) SNARE domain in astrocytes, in order to investigate if astrocytes play a role in sleep–wake regulation. They found that this genetic restriction of gliotransmission attenuated the build-up of sleep pressure, and prevented memory deficits associated with sleep loss. The data suggest an important role for astrocyte-derived adenosine in modulating cognitive consequences of sleep deprivation. Furthermore, the research team also conducted pharmacological studies and concluded that astrocytes modulate the accumulation of sleep pressure and its cognitive consequences through a pathway involving adenosine A_1 receptors (Halassa et al. 2009).

8 The Adenosine Receptor Antagonist Caffeine and Sleep-Loss-Associated Cognitive Impairments

Caffeine is the most widely consumed stimulant in the world. In the μM plasma concentrations reached after moderate consumption (Landolt et al. 1995; Carrier et al. 2007), caffeine acts as a non-selective, competitive antagonist at A_1 and A_{2A} receptors (Fredholm et al. 1999). Novel PET imaging findings suggest that intake of 4–5 cups of coffee (corresponding to ~450 mg caffeine) in a 70-kg volunteer can displace endogenous adenosine from 50 % of cerebral A_1 receptors (Elmenhorst et al. 2012). By contrast, other effects of caffeine observed in vitro, such as inhibition of phosphodiesterase, blockade of $GABA_A$ receptors and Ca^{2+} release, require more than 100 times higher doses than adenosine receptor antagonism and are toxic in humans (Fredholm 1995).

8.1 Caffeine Counteracts Sleep Deprivation-Induced Impaired Vigilant Attention by Interfering with Sleep Homeostasis

Various studies have examined the effects of caffeine on sustained attention in humans, via performance on the PVT. The psychostimulant has been consistently shown to reverse sleepiness and PVT impairments in sleepy humans (Landolt et al.

2004; Balkin et al. 2004; Kamimori et al. 2005; Rétey et al. 2006; Van Dongen et al. 2001; Wyatt et al. 2004; Landolt et al. 2012). Given that physiological doses of caffeine antagonize adenosine receptors, such findings are consistent with those of the aforementioned rodent study, which revealed decrements in vigilant performance following adenosine administration (Christie et al. 2008).

Wyatt and colleagues (2004) reflected that many studies investigating the neurobehavioral benefits of caffeine during sleep loss confounded the two major processes regulating sleep and wakefulness: the circadian phase and the duration of prior wakefulness (i.e., homeostatic sleep pressure). Specifically, previous research had not clarified if caffeine's ability to counteract performance deficits related to sleep deprivation was related to its interaction with circadian or homeostatic signals modulating sleep propensity and performance. The authors stress the importance of accounting for variance explained by sleep homeostatic and circadian modulation when interpreting data from protocols in which tests are given in only a single administration, such as typically occurs in traditional clinical and cognitive neuroscience research. As a result, the research team conducted a study to assess the effects of repeated low-dose caffeine administration during a 29-day forced desynchrony paradigm. The period of the sleep–wake cycle was scheduled to be 42.85 h (28.57-h wake episodes and 14.28-h sleep episodes), and thus far removed from the circadian range. This protocol allowed for separate quantification of the circadian, sleep homeostatic, and caffeine contributions to performance deficits and improvements. Moreover, the 42.85-h cycle simulated the extended wakefulness commonly encountered by medical and military personal, or anyone skipping a night of sleep (Wyatt et al. 2004).

During the study, caffeine was administered during wakefulness at a rate of 0.3 mg per kg per hour. The dosage schedule was designed to increase caffeine blood plasma concentrations in parallel to the rate of increase in sleep homeostatic drive during wakefulness, and also in line with the potential accumulation of adenosine (Porkka-Heiskanen et al. 2000). Polysomnographic recordings were used to monitor each scheduled sleep episode, as well as the majority of each wake episode, in order to detect incidences of slow eye movements and unintentional sleep onsets. During wake periods, mood, and subjective sleepiness were assessed at 30-min intervals using visual analog scales and the Karolinska Sleepiness Scale. Cognitive performance was tested every 2 h.

Post completion of the study, comparison of the placebo and caffeine data revealed that rising levels of caffeine significantly reduced wake-dependent deterioration in several measures of cognitive functioning, particularly at the circadian performance nadir (Wyatt et al. 2004). Specifically, caffeine attenuated performance deficits on the PVT such that the caffeine group showed fewer lapses and less impairment in the slowest 10 % of reaction times than the placebo group. Caffeine also enhanced the ability of subjects to remain consistently awake for extended periods. That is, the researchers observed inhibition of EEG-verified accidental sleep onsets during scheduled wake episodes. Such findings suggest that individuals receiving caffeine were kept at an earlier, less-severe stage of the sleep-onset continuum (Ogilvie et al. 1988), and this held them back from

completing the full transition to sleep. However, the caffeine group also showed impairment of polysomnographically verified sleep during scheduled sleep episodes. Subsequently, the additional sleep accumulated by the placebo group during scheduled wake and sleep episodes was associated with lower reports of sleepiness, independent of circadian phase, or duration of prior scheduled wakefulness. Indeed, subjects receiving caffeine self-reported greater impairment of alertness on the Karolinska Sleepiness Scale and visual analog scales. A similar paradoxical finding of increased subjective sleepiness in participants receiving caffeine over repeated days has been reported in other studies (Bonnet and Arand 1992). Thus, the wake-promoting effects of caffeine do not replace the restorative effects gained through sleep (Wyatt et al. 2004).

The evidence of a reduction in accidental sleep onsets during caffeine administration supports the concept that caffeine attenuates expression of homeostatic sleep drive. Because the plasma concentrations of caffeine reached in this study can be expected to affect solely adenosine receptors (Fredholm et al. 1999) and because caffeine primarily affects the sleep–wake-dependent modulation of performance, the present findings are in accordance with the proposed role for adenosine in mediating sleep–wake-dependent modulation of sleep propensity and associated variation in neurobehavioral functioning (Wyatt et al. 2004). While further research is required to elucidate whether mechanisms other than adenosine receptor antagonism or a certain degree of tolerance to caffeine over repeated administration could have influenced the experimental outcomes, repeated, low-dose caffeine administration holds potential as a countermeasure to cognitive deficits and unintended sleep attacks, at the cost of increasing subjective sleepiness.

8.2 Caffeine Ameliorates Deficits in Vigilant Attention from Sleep Inertia

Another study suggested that caffeine reduces impaired vigilant attention associated with sleep inertia under conditions of sleep loss. Sleep inertia refers to the impaired cognitive performance, grogginess, and tendency to fall back to sleep immediately after waking (Dinges and Orne 1981). Van Dongen and colleagues (2001) administered sustained low-dose caffeine (0.3 mg per kg per hour, except during naps) or placebo to healthy volunteers during the last 66 h of an 88-h period of extended wakefulness, which included seven 2-h naps during which polysomnographical recordings were made. Performance on the PVT was assessed every 2 h of wakefulness, and also during the sleep inertia experienced after awakening from naps. The results revealed that during the placebo condition, testing during sleep inertia was associated with significantly impaired psychomotor vigilance. By contrast, these performance decrements were absent in the caffeine condition. Thus, caffeine was shown to be an effective countermeasure to the impaired sustained attention seen during sleep inertia (Van Dongen et al. 2001).

Many people consume caffeine-containing beverages in the morning, directly after waking, at a time when their homeostatic sleep drive should be reduced. Thus, arguably, there should be no need to take the stimulant at this time of the day. Nevertheless, it is possible that following rapid awakening from NREM sleep, elevated levels of adenosine, and the corresponding existence of low vigilance and high sleepiness (Virus et al. 1983), could persist until adenosine is removed by reuptake or metabolism, and hence the phenomenon of sleep inertia (Van Dongen et al. 2001). In accordance with this hypothesis, sleep inertia does indeed seem to intensify with prior sleep loss (Dinges et al. 1985), and it is more pronounced when awakening occurs from NREM sleep, rather than from REM sleep (Broughton 1968; Bruck and Pisani 1999). The study of Van Dongen and colleagues (2001) involved less than 4 h of sleep per 24 h. Following the sleep periods, 85 % of awakenings occurred out of NREM sleep in the placebo condition, and subsequent deficits in psychomotor vigilance performance, due to sleep inertia, were consistently recorded. However, during the caffeine condition, sleep inertia after awakening from nap sleep was not apparent. Moreover, when psychomotor vigilance was tested between naps, as opposed to directly afterwards, there was no difference between performance in the two conditions. Such results imply that caffeine's effect was specific to sleep inertia. Overall, such findings are in accordance with the hypothesis that adenosine may be a neurobiological substrate of the sleep inertia phenomenon (Van Dongen et al. 2001).

8.3 Caffeine Reduces False Memories After Sleep Loss by Improving Arousal and Attention

Human memory is not an exact record of the world and our experiences, but instead is influenced by knowledge representations that already exist in the brain (Bartlett 1932). As a result, what is retrieved from memory can substantially differ from what was originally encoded (Schacter et al. 1998). For example, in some instances, people claim to remember events that in fact never happened. These false memories tend to be semantically linked to actually encoded events, and subjects are usually very confident about the correctness of these memories (Roediger and Mcdermott 1995). Schacter and colleagues (1998) suggest that the development of false memories involves the disruption of the same basic principles of memory formation as the development of correct memories. Memory formation involves three distinct stages: encoding (learning); consolidation (off-line processing and strengthening of memory traces after encoding); and retrieval of the learned material. Research has demonstrated that sleep deprivation may not only impair encoding and consolidation of memory, but also memory retrieval (Harrison and Horne 2000). Impaired memory retrieval associated with reduced source and reality monitoring may be involved in the generation of false memories, and consequently sleep deprivation would be expected to enhance their creation (Diekelmann et al. 2008). In a series of experiments, Diekelmann and colleagues (2008) investigated sleep-associated

mechanisms of false memory generation, using the well-established Deese, Roediger, McDermott false memory paradigm (Roediger and Mcdermott 1995). Here, subjects learned lists of semantically associated words (e.g., "night," "dark," "coal"). The strongest associate, however, or the "theme" of the list ("black" in this example), was not presented during learning. Subsequently, memory retrieval was tested 9, 33, or 44 h after learning. This involved the presentation of the previously viewed "list" words, together with the "theme" word (or "critical lure") and unrelated distracter words. Subjects were required to indicate whether a word had been presented during the learning phase or not. Immediately after learning the words, during the memory consolidation phase, participants either slept or stayed awake. At word retrieval, they were or were not acutely sleep deprived. The study revealed that when participants were sleep deprived during retrieval of stored words, there was a significant increase in the number of false memories of theme words. That is, they reported that they had been presented with a specific word during the learning phase, when in fact they had not. Of particular relevance to the present discussion was the finding that this distortion of memory was removed by administering caffeine to the sleep deprived subjects prior to retrieval testing. Such evidence indicates that adenosinergic mechanisms are involved in the depletion of specific cognitive resources, which elicits the generation of false memories associated with sleep loss (Diekelmann et al. 2008). It is possible that caffeine improved reduced arousal and sustained attention after sleep deprivation, which rely on a prefrontal-parietal network, basal forebrain, and thalamus, and are known to be implicated in memory functions.

8.4 Caffeine has Weak Potency to Improve Impaired Higher-Order and Executive Functions After Sleep Deprivation

Much research regarding the effects of caffeine on performance during sleep deprivation has focused primarily on measures of simple cognitive processes, as opposed to memory and executive functions. Yet, if a subjective state or cognitive function is impaired by sleep loss, then it may be expected that this decrement would be reversed by caffeine (Wyatt et al. 2004). To test this hypothesis, Wyatt and colleagues (2004) not only studied the effects of caffeine on PVT performance during forced desynchrony, but also assessed short-term memory (Probed Recall Memory Task) and cognitive throughput (Addition Task, Digit Symbol Substitution Task). Indeed, caffeine tended to reduce the wake-dependent impairment of short-term memory and attenuated performance deficits in the two cognitive throughput tasks when compared to placebo. Thus, the potential benefits of caffeine on higher-order cognitive performance warrant further investigation.

Killgore and colleagues (2012) performed an investigation into the potential benefits of stimulants on decision making during sleep deprivation. The protocol

required subjects to perform the IGT at four time points throughout a period comprising 61 h of sleep deprivation and 12 h of recovery sleep. After 44 h of wakefulness, participants received a double-blind administration of caffeine (600 mg), d-amphetamine (20 mg), modafinil (400 mg), or placebo. As predicted, sleep deprivation was found to alter normal decision making, which was consistent with the team's previous research (Killgore et al. 2006, 2007b). Yet, perhaps the most important finding was the fact that although all three stimulants were highly effective at reducing subjective sleepiness and sustaining psychomotor vigilance relative to placebo, none of the pharmacologic agents provided any significant enhancement of decision-making performance on the IGT. In fact, performance was similar to placebo for all stimulant groups (Killgore et al. 2012). It should be noted here that IGT performance was unrelated to self-reported sleepiness or psychomotor vigilance performance during the administration of the stimulants, which implies that the deficits observed in decision making were independent of differences in alertness. That is, despite subjects on stimulants being awake, alert, and able to sustain psychomotor vigilance, they were not any better than placebo on the IGT (Killgore et al. 2012). These findings are consistent with a previous study which evaluated the effect of caffeine on sleep-deprived IGT performance (Killgore et al. 2007b). In that study, repeated doses of caffeine (200 mg every 2 h) during the overnight sessions, up to 3 h before each IGT, had virtually no effect on performance relative to placebo at either 51 or 75 h of sleep deprivation. Similarly, caffeine had no significant effect on the time taken for subjects to make various types of moral judgments after 53 h of prolonged wakefulness (Killgore et al. 2007b).

In fact, other studies have also reported limited effects of various stimulants on higher-order cognition and executive functions during sleep loss. For example, Gottselig and colleagues (2006) revealed that caffeine was effective at restoring simple aspects of cognitive functioning, such as attention. Yet, the stimulant failed to restore a more complex aspect of executive function, random number generation (Brugger et al. 1996), a cognitive process that relies on the prefrontal cortex (Gottselig et al. 2006).

Some evidence indicates that the effectiveness of stimulants, including caffeine, on executive functions may be task-specific, and depend upon the underlying executive function systems targeted by different stimulant (Killgore et al. 2009). For instance, participants' performance on a behavioral measure of risk-taking and impulsive responding (the Balloon Analog Risk Task) was relatively resistant to the effects of sleep loss until about 75 h of continuous wakefulness, at which point there was a clear increase in risky decision making (Killgore et al. 2011). It is noteworthy that caffeine appeared to mitigate this surge in risk-taking at extreme sleep deprivation (Killgore et al. 2011). This finding suggests that the types of executive functions measured by the Iowa Gambling Task, the random number generation task, and the Balloon Analog Risk Task may involve different brain systems that are differentially affected by caffeine, and thus adenosinergic mechanisms.

9 Inter-Individual Differences in the Effects of Caffeine

More recently, there has been increased interest in inter-individual differences in the impairment of neurobehavioral functions from sleep loss and in the effectiveness of common pharmacological countermeasures such as caffeine. The clarification of the mechanisms underlying these differences is relevant because they would reveal insights into the neurophysiological regulation of human wakefulness and sleep. Moreover, they are also of clinical importance because they may highlight individuals at greater risk for impaired neurobehavioral performance and reduced health associated with prolonged wakefulness and shift work (Rajaratnam and Arendt 2001). In humans, sleep loss produces a range of cognitive deficits, including reduction in vigilance, working memory, and executive function. Yet, there are large inter-individual differences in these deficits, which account for a substantial portion of the variance. In a study involving repeated exposure to sleep deprivation under controlled laboratory conditions, Van Dongen and colleagues (2004) demonstrated that sleep loss negatively influences measures of subjective sleepiness, fatigue and mood, behavioral alertness (sustained attention), and cognitive processing capability (working memory). While these impairments were stable within individuals, there were significant differences among individuals that were not merely a consequence of a different sleep history. Thus, the authors suggested that these individual differences represented trait-like differential vulnerability to sleep loss.

9.1 Adenosinergic Mechanisms Contribute to Inter-Individual Differences in Vigilant Attention During Prolonged Wakefulness

Given the evidence discussed above, Rétey and colleagues (2006) predicted that adenosinergic mechanisms play a role for inter-individual differences in neurobehavioral function during prolonged wakefulness. To test this hypothesis, the research team investigated the combined effects of sleep deprivation and caffeine on PVT speed and EEG activity in individuals that rated themselves as either caffeine-sensitive or caffeine-insensitive. It was previously suggested that subjective differences in the psychostimulant effects of caffeine might reflect genetically determined differences in the adenosinergic system (Alsene et al. 2003; Goldstein et al. 1965). Thus, it was hypothesized that subjects from both ends of the caffeine-sensitivity spectrum would not only react differently to caffeine, but also show different sleep-deprivation induced changes in neurobehavioral function and the EEG (Rétey et al. 2006). The study protocol required the 12 subjectively caffeine-sensitive and 10 caffeine-insensitive subjects to complete two experimental blocks separated by 1 week. Each block consisted of 4 nights and 2 days in the sleep laboratory. After 2 consecutive, 8-h, nocturnal sleep recordings

(comprising an "adaptation" night and baseline assessment), the subjects were kept awake for 40 h under constant supervision by members of the research team. During this period of prolonged wakefulness, EEG topography was assessed every 3 h, as well as PVT and random number generation performance. After both 11 and 23 h of sleep deprivation, participants received a capsule with either 200 mg caffeine or placebo, according to a randomized, double-blind, cross-over design. Finally, a 10.5-h recovery night was followed by a final waking EEG, PVT, and random number generation assessment.

Analysis of the results revealed that while there were no differences at baseline in optimal PVT performance (i.e., the fastest 10th percentile of reaction times) between subjectively caffeine-sensitive and caffeine-insensitive men, there were differences in the regional EEG power distribution between these groups in the theta range in waking after a baseline night of sleep. These differences were enhanced by sleep deprivation in the antero-posterior power gradients in the waking EEG, and also induced differences in the PVT (Rétey et al. 2006). Here, prolonged wakefulness impaired PVT speed more in self-rated caffeine-sensitive individuals than in caffeine-insensitive individuals. Such observations are in accordance with functional imaging studies indicating that the vulnerability to sleep deprivation-induced performance decline in working memory is linked with baseline differences in task-related cortical activation (Mu et al. 2005). Taken together, the findings suggest that physiological variables recorded during baseline assessment could be useful future predictors of individual vulnerability to sleep deprivation.

Importantly, caffeine counteracted the sleep-loss-induced PVT differences between the two groups of subjects. Moreover, correlation analyses revealed that those individuals with the largest neurobehavioral impairment from sleep deprivation benefited the most from the stimulant action of caffeine. Interestingly, optimal PVT performance has been shown to activate a cortical-sustained attention network and the motor system including the striatum (Drummond et al. 2005a). This region shows prominent expression of adenosine A_{2A} receptors (Fig. 3b) (Bauer and Ishiwata 2009). Furthermore, this adenosine receptor subgroup was shown to be responsible for the wakefulness-promoting effect of caffeine (Huang et al. 2005; Lazarus et al. 2011), and a common c.1976$T > C$ polymorphism of the A_{2A} receptor gene has been associated with inter-individual differences in EEG theta power during wakefulness and sleep (Rétey et al. 2005). Therefore, Rétey and colleagues suggested that this adenosine receptor subtype plays a role in determining the differences between individuals in their vulnerability to impairments of neurobehavioral performance following sleep loss (Rétey et al. 2006). Indeed, recent preliminary findings indicate that the c.1976$T > C$ polymorphism of *ADORA2A* impacts neurobehavioral performance during sleep restriction (Rupp et al. 2013).

With regard to the EEG topography data, this study found that the overall effect of sleep loss on the waking EEG was consistent with previous studies (Cajochen et al. 2001). Yet, there were noteworthy differences between the individuals which emerged following analysis of regional power distributions between fronto-central and parieto-occipital EEG derivations. Specifically, both the effects of sleep loss and caffeine on antero-posterior power gradients in the theta range tended to be

more prominent in caffeine-sensitive subjects than in caffeine-insensitive participants. These differences mirrored the inter-individual differences in the effects of sleep deprivation and caffeine on sustained vigilant attention. Here it may be important to remember that frontal theta activity reflects the alternative activation of brain regions linked with continuous attention—the prefrontal cortex and anterior cingulate cortex (Asada et al. 1999). Moreover, a combined EEG and fMRI study highlighted a positive correlation between theta activity (5–9.5 Hz range) in waking and the fMRI signal of the right dorso-lateral prefrontal and superior parietal cortices (Foucher et al. 2004). In accordance with the interpretation that these areas are involved in arousal, as well as the maintenance of attention, it has also been reported that optimal PVT speed after sleep deprivation depends on activation of a fronto-parietal sustained attention network and frontal cortical regions (Drummond et al. 2005a). Rétey and colleagues (2006) thus propose that their EEG data support brain imaging studies which show that changes in activation after sleep deprivation in fronto-parietal regions are related to individual differences in attentional impairment from sleep loss, and moreover, that adenosinergic mechanisms may contribute to these differences.

9.2 *Polymorphisms of ADORA2A Modulate the Individual Response to Caffeine After Sleep Deprivation*

More recent researches have demonstrated that in humans, genetic variation of the adenosine A_{2A} receptor gene, *ADORA2A*, mediates an individuals' susceptibility to panic disorder and individual differences in anxiety-related personality, habitual caffeine consumption, and arousal (Cornelis et al. 2007; Deckert et al. 1998; Hamilton et al. 2004; Hohoff et al. 2010). Furthermore, individual anxiogenic and sleep-disrupting responses to caffeine have been consistently associated with the common *C*-to-*T* substitution at nucleotide 1976 of *ADORA2A* (Alsene et al. 2003; Childs et al. 2008; Rétey et al. 2007; Rogers et al. 2010). The *T*-allele of this polymorphism predisposes Caucasian individuals to anxiety following caffeine consumption (Alsene et al. 2003; Childs et al. 2008; Rogers et al. 2010), while the *C*-allele seems to relay a tendency toward disturbed sleep following ingestion of the stimulant (Rétey et al. 2007).

In a recent publication, Bodenmann and colleagues (2012) examined the effects of genetic variation of *ADORA2A* and sleep deprivation on subjective sleepiness, PVT, waking and sleep EEG, and the pharmacogenetic response to the stimulants caffeine and modafinil. The study revealed that the carriers of a distinct *ADORA2A* haplotype (haplotype HT4—these individuals carry a *T*-allele at nucleotide 1976) showed greater vigilance during sleep loss than carriers of non-HT4 haplotype alleles (Fig. 4b). Furthermore, caffeine did not counteract the consequences of prolonged wakefulness on psychomotor speed and EEG delta activity in the carriers of haplotype HT4. On the other hand, modafinil, which does not interact with A_{2A} receptors, influenced the effects of prolonged wakefulness irrespective of

ADORA2A haplotype. It was concluded that genetic variation of *ADORA2A* not only affects psychomotor response speed, but also modulates the effects of caffeine on neurobehavioral and neurophysiological aspects of sleep–wake regulation (Bodenmann et al. 2012).

10 Conclusions

Consistent findings accumulated over the past few decades which suggest that attentional performance is particularly sensitive to time of day modulations and the effects of sleep loss. Efferent projections from the circadian master clock located in the SCN form connections to the dorso-medial hypothalamus, which sends out afferents to cholinergic and monoaminergic neurons in BF, brainstem, and hypothalamic nuclei involved in promoting behavioral arousal, attention, and cortical activation. The "sleep substance," adenosine, is released in activity-dependent manner and activates A_1 and A_{2A} receptors located in these and other brain regions, including basal ganglia and cortex. Adenosine induces global cortical disfacilitation by reducing the activating input from the ascending arousal pathways and actively excites sleep-active neurons in the ventro-lateral-preoptic area of the hypothalamus. We, thus, conclude that adenosine contributes to the regulation of brain functions modulated by the sleep–wake cycle, in particular to sleepiness and sustained attention which are heavily affected by sleep loss. Indeed, convergent pharmacologic and genetic data in animals and humans support the notion that differences in adenosinergic tone in the central nervous system affect vigilant attention. The differences appear to be present in rested and sleep-deprived states and do not reflect different accumulation of homeostatic sleep pressure during extended wakefulness or differential vulnerability to the effects of sleep loss.

Further support for a role for adenosine in modulating sleep pressure and associated variation in arousal and attention stems from the effects of the adenosine receptor antagonist, caffeine. Acute and repeated administration of the stimulant attenuate subjective, neurophysiological and neurobehavioral consequences of moderate acute sleep deprivation. It is evident, however, that caffeine cannot substitute for sleep, and commonly consumed doses of the stimulant do not improve higher-order cognitive functions that are compromised after severe sleep loss. These findings indicate that adenosinergic mechanisms may be particularly important for the initial effects of sleep deprivation and that additional mechanisms contribute to the cognitive consequences of severe sleep deficits.

Caffeine is a non-selective A_1 and A_{2A} receptor antagonist, and these two adenosine receptor subtypes may play different roles in sleep–wake associated brain functions. Recent studies in knock-out animals suggest that the psychostimulant and the arousal effects of the xanthine are mainly mediated by A_{2A} receptors. This conclusion is supported by findings in humans showing that

common genetic variation of *ADORA2A* determines individual effects of caffeine on vigilant attention during sleep deprivation. The findings demonstrate a role for A_{2A} receptors in the effects of prolonged wakefulness on vigilant attention.

11 Perspectives

Further research will aim at elucidating the involvement of adenosine in downstream mechanisms underlying sleep deprivation-induced impairment of cognitive functions and synaptic plasticity. Recent evidence indicates that changes in adenosine during prolonged wakefulness are implicated in plasticity deficits (Dias et al. 2013). Neuronal and glial-derived adenosine may lead to increased sleepiness after sleep loss and signal an increased need for sleep to balance adenosine. Thus, sleep may serve to counteract overstimulation of the brain and excitotoxicity associated with prolonged wakefulness. Adenosine reduces excitatory neurotransmission by stimulating inhibitory A_1 receptors. The A_1 receptor appears to be required for disruption of hippocampal long-term potentiation by a spontaneous low-frequency EEG pattern, which is typical for deep NREM sleep and could provide a stimulus for plasticity reversal (Dias et al. 2013). Prolonged A_1 receptor activation also induces dynamic changes in the synaptic expression of *N*-Methyl-D-aspartic acid (NMDA) receptors that may reversibly adjust the threshold for plasticity induction (Kopp et al. 2006).

On the other hand, adenosine actively promotes sleep by stimulating excitatory A_{2A} receptors in ventro-lateral preoptic area of the hypothalamus. Activation of A_{2A} receptors by endogenous adenosine is required for hippocampal long-term potentiation by brain-derived neurotrophic factor (BDNF), an established marker of activity-dependent neuronal plasticity (Fontinha et al. 2008). Cortical *Bdnf* in rats is higher after wakefulness than after sleep and increased after sleep deprivation (Conti et al. 2007). Chronic caffeine treatment appears to preserve the levels of BDNF in the sleep-deprived brain (Alhaider et al. 2011). Finally, A_{2A} receptors co-localize with metabotropic glutamate receptors of subtype 5 (mGluR5), which induce BDNF expression and stimulate gliotransmission. The mGluR5 are primarily expressed on post-synaptic neurons and glia cells and contribute importantly to long-term depression (Izumi and Zorumski 2012), but also to long-term potentiation. It was recently found that sleep loss increases mGluR5 availability in the human brain, and this increase was closely correlated with increased sleepiness after a night without sleep (Hefti et al. 2013).

Whereas many studies investigated the effects of caffeine on the sleep-deprived brain, the possible roles for adenosine, adenosine receptor subtypes, and effects of caffeine in genetically distinct animals and humans on sleep–wake-related neuronal plasticity have only started to be explored. It is suggested that the further development of this avenue of research will permit a better understanding of sleep as a fundamental brain process. This knowledge may then lead to the rational development of more effective treatment and countermeasure strategies, not only of

impaired vigilance and attentional processes but also of reduced higher-order cognitive functions, in conditions of sleep deprivation, shiftwork, and jet-lag, for example. Such strategies are highly important for public health and personal safety.

References

Achermann P, Borbély AA (2011) Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. Elsevier Saunders, St. Louis, pp 431–444

Alhaider IA, Aleisa AM, Tran TT, Alkadhi KA (2011) Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. Mol Cell Neurosci 46:742–751

Alsene K, Deckert J, Sand P, de Wit H (2003) Association between A(2a) receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 28:1694–1702

Asada H, Fukuda Y, Tsunoda S, Yamaguchi M, Tonoike M (1999) Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. Neurosci Lett 274:29–32

Aston-Jones G (2005) Brain structures and receptors involved in alertness. Sleep Med 6:S3–S7

Aston-Jones G, Chen S, Zhu Y, Oshinsky ML (2001) A neural circuit for circadian regulation of arousal. Nat Neurosci 4:732–738

Bachmann V, Klaus F, Bodenmann S, Schäfer N, Brugger P, Huber S, Berger W, Landolt H-P (2012) Functional ADA polymorphism increases sleep depth and reduces vigilant attention in humans. Cereb Cortex 22:962–970

Balkin TJ, Bliese PD, Belenky G, Sing H, Thorne DR, Thomas M, Redmond DP, Russo M, Wesensten NJ (2004) Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. J Sleep Res 13:219–227

Bartlett FC (1932) Remembering: a study in experimental and social psychology. Cambridge University Press, Cambridge

Basheer R, Strecker RE, Thakkar MM, McCarley RW (2004) Adenosine and sleep-wake regulation. Prog Neurobiol 73:379–396

Battistuzzi G, Iudicone P, Santolamazza P, Petrucci R (1981) Activity of adenosine deaminase allelic forms in intact erythrocytes and in lymphocytes. Ann Hum Genet 45:15–19

Bauer A, Ishiwata K (2009) Adenosine receptor ligands and PET imaging of the CNS. In: Wilson CN, Mustafa SJ (eds) Handbook of experimental pharmacology (adenosine receptors in health and disease). Springer, Berlin, pp 617–642

Baxter MG, Chiba AA (1999) Cognitive functions of the basal forebrain. Curr Opin Neurobiol 9:178–183

Bechara A (2004) The role of emotion in decision-making: evidence from neurological patients with orbitofrontal damage. Brain Cogn 55:30–40

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15

Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ (2003) Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. J Sleep Res 12:1–12

Bjorness TE, Kelly CL, Gao TS, Poffenberger V, Greene RW (2009) Control and function of the homeostatic sleep response by adenosine A(1) receptors. J Neurosci 29:1267–1276

Blanco-Centurion C, Xu M, Murillo-Rodriguez E, Gerashchenko D, Shiromani AM, Salin-Pascual RJ, Hof PR, Shiromani PJ (2006) Adenosine and sleep homeostasis in the basal forebrain. J Neurosci 26:8092–8100

Bodenmann S, Landolt HP (2010) Effects of modafinil on the sleep EEG depend on Val158Met genotype of COMT. Sleep 33:1027–1035

Bodenmann S, Hohoff C, Freitag C, Deckert J, Rétey JV, Bachmann V, Landolt H-P (2012) Polymorphisms of ADORA2A modulate psychomotor vigilance and the effects of caffeine on neurobehavioral performance and sleep EEG after sleep deprivation. Br J Pharmacol 165:1904–1913

Bonnet MH (2000) Sleep deprivation. In: Kryger MH, Rothman N, Dement WC (eds) Principles and practice of sleep medicine. Saunders Company, Philadelphia, pp 53–71

Bonnet MH, Arand DL (1992) Caffeine use as a model of acute and chronic insomnia. Sleep 15:526–536

Borbély AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195–204

Brooks DJ, Doder M, Osman S, Luthra SK, Hirani E, Hume S, Kase H, Kilborn J, Martindill S, Mori A (2008) Positron emission tomography analysis of [C-11] KW-6002 binding to human and rat adenosine A(2A) receptors in the brain. Synapse 62:671–681

Broughton RJ (1968) Sleep disorders: disorders of arousal. Science 159:1070–1078

Bruck D, Pisani DL (1999) The effects of sleep inertia on decision-making performance. J Sleep Res 8:95–103

Brugger P, Monsch AU, Salmon DP, Butters N (1996) Random number generation in dementia of the Alzheimer type: a test of frontal executive functions. Neuropsychologia 34:97–103

Cajochen C, Brunner DP, Kräuchi K, Graw P, Wirz-Justice A (1995) Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. Sleep 18:890–894

Cajochen C, Khalsa SBS, Wyatt JK, Czeisler CA, Dijk D-J (1999) EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. Am J Physiol 277:R640–R649

Cajochen C, Knoblauch V, Kräuchi K, Renz C, Wirz-Justice A (2001) Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure. NeuroReport 12:2277–2281

Cajochen C, Blatter K, Wallach D (2004) Circadian and sleep-wake dependent impact on neurobehavioral function. Psychol Belg 44:59–80

Cajochen C, Chellappa S, Schmidt C (2010) What keeps us awake?-the role of clocks and hourglasses, light, and melatonin. Sci Awaken 93:57–90

Carrier J, Monk TH (2000) Circadian rhythms of performance: new trends. Chronobiol Int 17:719–732

Carrier J, Fernandez-Bolanos M, Robillard R, Dumont M, Paquet J, Selmaoui B, Filipini D (2007) Effects of caffeine are more marked on daytime recovery sleep than on nocturnal sleep. Neuropsychopharmacology 32:964–972

Childs E, Hohoff C, Deckert J, Xu K, Badner J, de Wit H (2008) Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 33:2791–2800

Christie MA, Bolortuya Y, Chen LC, McKenna JT, McCarley RW, Strecker RE (2008) Microdialysis elevation of adenosine in the basal forebrain produces vigilance impairments in the rat psychomotor vigilance task. Sleep 31:1393–1398

Colquhoun P (1981) Handbook of behavioural neurobiology. Plenum Press, New York

Conti B, Maier R, Barr AM, Morale MC, Lu X, Sanna PP, Bilbe G, Hoyer D, Bartfai T (2007) Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. Mol Psychiatry 12:167–189

Cordova CA, Said BO, McCarley RW, Baxter MG, Chiba AA, Strecker RE (2006) Sleep deprivation in rats produces attentional impairments on a 5-choice serial reaction time task. Sleep 29:69–76

Cornelis MC, El-Sohemy A, Campos H (2007) Genetic polymorphism of the adenosine A_{2A} receptor is associated with habitual caffeine consumption. Am J Clin Nutr 86:240–244

Damasio AR (1994) Descartes' error: emotion, reason and the human brain. Grosset/Putman, New York

Dang-Vu TT, Schabus M, Desseilles M, Sterpenich V, Bonjean M, Maquet P (2010) Functional neuroimaging insights into the physiology of human sleep. Sleep 33:1589–1603

Deckert J, Nothen MM, Franke P, Delmo C, Fritze J, Knapp M, Maier W, Beckmann H, Propping P (1998) Systematic mutation screening and association study of the A_1 and A_{2a} adenosine receptor genes in panic disorder suggest a contribution of the A_{2a} gene to the development of disease. Mol Psychiatry 3:81–85

Dias RB, Rombo DM, Ribeiro JA, Henley JM, Sebastiao AM (2013) Adenosine: setting the stage for plasticity. Trends Neurosci 36:248–257

Dickinson DL, Drummond SPA (2008) The effects of total sleep deprivation on bayesian updating. Judgment Decis Making 3:181–190

Diekelmann S, Landolt HP, Lahl O, Born J, Wagner U (2008) Sleep loss produces false memories. Plos One 3:e3512

Dijk DJ, Archer SN (2009) Circadian and homeostatic regulation of human sleep and cognitive performance and its modulation by PERIOD3. In: Lee-Chiong T (ed) Circadian rhythm sleep disorders (sleep medicine clinics). Saunders, Philadelphia, pp 111–125

Dijk DJ, Czeisler CA (1994) Paradoxical timing of the circadian-rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. Neurosci Lett 166:63–68

Dijk D-J, Czeisler CA (1995) Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15:3526–3538

Dinges DF, Orne M (1981) Performance after naps in sleep-conducive and alerting environments. In: Johnson D, Tepas D, Colquhoun P, Colligan M (eds) Biological rhythms, sleep and shift work. Springer, New York, pp 539–552

Dinges DF, Powell JW (1985) Microcomputer analyses of performance on a portable, simple visual reaction task during sustained operations. Behav Res Methods Instrum Comput 17:652–655

Dinges DF, Orne MT, Orne EC (1985) Assessing performance upon abrupt awakening from naps during quasi-continuous operations. Behav Res Methods Instrum Comput 17:37–45

Doran SM, Van Dongen HP, Dinges DF (2001) Sustained attention performance during sleep deprivation: evidence of state instability. Arch Ital Biol 139:253–267

Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB (2000) Altered brain response to verbal learning following sleep deprivation. Nature 403:655–657

Drummond SP, Bischoff-Grethe A, Dinges DF, Ayalon L, Mednick SC, Meloy MJ (2005a) The neural basis of the psychomotor vigilance task. Sleep 28:1059–1068

Drummond SPA, Meloy MJ, Yanagi MA, Off HJ, Brown GG (2005b) Compensatory recruitment after sleep deprivation and the relationship with performance. Psychiatry Res Neuroimaging 140:211–223

Drummond SPA, Paulus MP, Tapert SF (2006) Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. J Sleep Res 15:261–265

Duffy JF, Rimmer DW, Czeisler CA (2001) Association of intrinsic circadian period with morningness–eveningness, usual wake time, and circadian phase. Behav Neurosci 115:895–899

Elmenhorst D, Meyer PT, Winz OH, Matusch A, Ermert J, Coenen HH, Basheer R, Haas HL, Zilles K, Bauer A (2007) Sleep deprivation increases A(1) adenosine receptor binding in the human brain: a positron emission tomography study. J Neurosci 27:2410–2415

Elmenhorst D, Basheer R, McCarley RW, Bauer A (2009) Sleep deprivation increases A(1) adenosine receptor density in the rat brain. Brain Res 1258:53–58

Elmenhorst D, Meyer PT, Matusch A, Winz OH, Bauer A (2012) Caffeine occupancy of human cerebral A_1 adenosine receptors: in vivo quantification with ^{18}F-CPFPX and PET. J Nucl Med (in press)

Finelli LA, Baumann H, Borbély AA, Achermann P (2000) Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. Neuroscience 101:523–529

Folkard S (1975) Diurnal-variation in logical reasoning. Br J Psychol 66:1–8

Folkard S, Wever RA, Wildgruber CM (1983) Multi-oscillatory control of circadian-rhythms in human-performance. Nature 305:223–226

Fontinha BM, Diogenes MJ, Ribeiro JA, Sebastiao AM (2008) Enhancement of long-term potentiation by brain-derived neurotrophic factor requires adenosine A(2A) receptor activation by endogenous adenosine. Neuropharmacology 54:924–933

Foucher JR, Otzenberger H, Gounot D (2004) Where arousal meets attention: a simultaneous fMRI and EEG recording study. Neuroimage 22:688–697

Franks NP (2008) General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nature Rev Neurosci 9:370–386

Fredholm BB (1995) Adenosine, adenosine receptor and the action of caffeine. Pharmacol Toxicol 76:93–101

Fredholm BB, Bättig K, Holmen J, Nehlig A, Zvartau EE (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev 51:83–133

Fredholm BB, Chen JF, Cunha RA, Svenningsson P, Vaugeois JM (2005) Adenosine and brain function. Int Rev Neurobiol 63:191–270

Gallopin T, Luppi PH, Cauli B, Urade Y, Rossier J, Hayaishi O, Lambolez B, Fort P (2005) The endogenous somnogen adenosine excites a subset of sleep-promoting neurons via A2A receptors in the ventrolateral preoptic nucleus. Neuroscience 134:1377–1390

Gillberg M, Kecklund G, Akerstedt T (1994) Relations between performance and subjective ratings of sleepiness during a night awake. Sleep 17:236–241

Goldstein A, Warren R, Kaizer S (1965) Psychotropic effects of caffeine in man. I. Individual differences in sensitivity to caffeine-induced wakefulness. J Pharmacol Exp Ther 149:156–159

Gottselig JM, Adam M, Rétey JV, Khatami R, Achermann P, Landolt H-P (2006) Random number generation during sleep deprivation: effects of caffeine on response maintenance and stereotypy. J Sleep Res 15:31–40

Graw P, Kräuchi K, Knoblauch V, Wirz-Justice A, Cajochen C (2004) Circadian and wake-dependent modulation of fastest and slowest reaction times during the psychomotor vigilance task. Physiol Behav 80:695–701

Hagewoud R, Bultsma LJ, Barf RP, Koolhaas JM, Meerlo P (2011) Sleep deprivation impairs contextual fear conditioning and attenuates subsequent behavioural, endocrine and neural responses. J Sleep Res 20:259–266

Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG (2009) Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61:213–219

Hamilton SP, Slager SL, De Leon AB, Heiman GA, Klein DF, Hodge SE, Weissman MM, Fyer AJ, Knowles JA (2004) Evidence for genetic linkage between a polymorphism in the adenosine 2A receptor and panic disorder. Neuropsychopharmacology 29:558–565

Harrison Y, Horne JA (2000) The impact of sleep deprivation on decision making: A review. J Exp Psychol Appl 6:236–249

Harrison Y, Jones K, Waterhouse J (2007) The influence of time awake and circadian rhythm upon performance on a frontal lobe task. Neuropsychologia 45:1966–1972

Hayaishi O, Urade Y, Eguchi N, Huang Z-L (2004) Genes for prostaglandin D synthase and receptor as well as adenosine A_{2A} receptor are involved in the homeostatic regulation of NREM sleep. Arch Ital Biol 142:533–539

Haydon PG, Carmignoto G (2006) Astrocyte control of synaptic transmission and neurovascular coupling. Physiol Rev 86:1009–1031

Hefti K, Holst SC, Sovago J, Bachmann V, Buck A, Ametamey SM, Scheidegger M, Bethold T, Gomez-Mancilla B, Seifritz E, Landolt HP (2013) Increased metabotropic glutamate receptor subtype 5 availability in human brain after one night without sleep. Biol Psychiatry 73:161–168

Hirschhorn R, Yang DR, Israni A (1994) An Asp8Asn substitution results in the adenosine deaminase (ADA) genetic polymorphism (ADA 2 allozyme): occurrence on different chromosomal backgrounds and apparent intragenic crossover. Ann Hum Genet 58:1–9

Hohoff C, Mullings EL, Heatherley SV, Freitag CM, Neumann LC, Domschke K, Krakowitzky P, Rothermundt M, Keck ME, Erhardt A, Unschuld PG, Jacob C, Fritze J, Bandelow B, Maier W, Holsboer F, Rogers PJ, Deckert J (2010) Adenosine A_{2A} receptor gene: evidence for association of risk variants with panic disorder and anxious personality. J Psychiatry Res 44:930–937

Horne JA (1988) Sleep loss and "divergent" thinking ability. Sleep 11:528–536

Horne JA, Östberg O (1976) A self-assessment questionnaire to determine morningness–eveningness in human circadian rhythms. Int J Chronobiol 4:97–110

Huang ZL, Qu WM, Eguchi N, Chen JF, Schwarzschild MA, Fredholm BB, Urade Y, Hayaishi O (2005) Adenosine A_{2A}, but not A_1, receptors mediate the arousal effect of caffeine. Nature Neurosci 8:858–859

Izumi Y, Zorumski CF (2012) NMDA receptors, mGluR5, and endocannabinoids are involved in a cascade leading to hippocampal long-term depression. Neuropsychopharmacology 37:609–617

Kamimori GH, Johnson D, Thorne D, Belenky G (2005) Multiple caffeine doses maintain vigilance during early morning operations. Aviat Space Environ Med 76:1046–1050

Killgore WDS (2010) Effects of sleep deprivation on cognition. Human Sleep and Cognition, Part I: Basic Research 185:105–129

Killgore WDS, Balkin TJ, Wesensten NJ (2006) Impaired decision making following 49 h of sleep deprivation. J Sleep Res 15:7–13

Killgore WDS, Killgore DB, Day LM, Li C, Kamimori GH, Balkin TJ (2007a) The effects of 53 hours of sleep deprivation on moral judgment. Sleep 30:345–352

Killgore WDS, Lipizzi EL, Kamimori GH, Balkin TJ (2007b) Caffeine effects on risky decision making after 75 hours of sleep deprivation. Aviat Space Environ Med 78:957–962

Killgore WDS, Kahn-Greene ET, Grugle NL, Killgore DB, Balkin TJ (2009) Sustaining executive functions during sleep deprivation: a comparison of caffeine, dextroamphetamine, and modafinil. Sleep 32:205–216

Killgore WDS, Kamimori GH, Balkin TJ (2011) Caffeine protects against increased risk-taking propensity during severe sleep deprivation. J Sleep Res 20:395–403

Killgore WDS, Grugle NL, Balkin TJ (2012) Gambling when sleep deprived: don't bet on stimulants. Chronobiol Int 29:43–54

Kleitman N, Titelbaum S, Feiveson P (1938) The Effect of Body Temperature on Reaction Time. Am J Physiol 121:495–501

Kopp C, Longordo F, Nicholson JR, Lüthi A (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. J Neurosci 26:12456–12465

Krueger JM, Rector DM, Roy S, Van Dongen HPA, Belenky G, Panksepp J (2008) Sleep as a fundamental property of neuronal assemblies. Nature Rev Neurosci 9:910–919

Krueger JM, Taishi P, De A, Davis CJ, Winters BD, Clinton J, Szentirmai E, Zielinski MR (2010) ATP and the purine type 2 $\times$ 7 receptor affect sleep. J Appl Physiol 109:1318–1327

Laird DA (1925) Relative performance of college students as conditioned by time of day and day of week. J Exp Psychol 8:50–63

Landolt HP (2008) Sleep homeostasis: a role for adenosine in humans? Biochem Pharmacol 75:2070–2079

Landolt HP (2012) "No thanks, coffee keeps me awake": individual caffeine sensitivity depends on ADORA2A genotype. Sleep 35:899–900

Landolt HP, Dijk DJ, Gaus SE, Borbély AA (1995) Caffeine reduces low-frequency delta activity in the human sleep EEG. Neuropsychopharmacology 12:229–238

Landolt HP, Rétey JV, Tönz K, Gottselig JM, Khatami R, Buckelmüller I, Achermann P (2004) Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. Neuropsychopharmacology 29:1933–1939

Landolt HP, Rétey JV, Adam M (2012) Reduced neurobehavioral impairment from sleep deprivation in older adults: contribution of adenosinergic mechanisms. Front Neurol 3:62
Lavie P (2001) Sleep-wake as a biological rhythm. Ann Rev Psychol 52:277–303
Lazarus M, Shen HY, Cherasse Y, Qu WM, Huang ZL, Bass CE, Winsky-Sommerer R, Semba K, Fredholm BB, Boison D, Hayaishi O, Urade Y, Chen JF (2011) Arousal effect of caffeine depends on adenosine A(2A) receptors in the shell of the nucleus accumbens. J Neurosci 31:10067–10075
Leproult R, Colecchia EF, Berardi AM, Stickgold R, Kosslyn SM, Van Cauter E (2003) Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. Am J Physiol 284:R280–R290
Li XR, Lu ZL, D'Argembeau A, Ng M, Bechara A (2010) The Iowa gambling task in fMRI images. Hum Brain Mapp 31:410–423
Lim JL, Dinges DF (2008) Sleep deprivation and vigilant attention. Ann N Y Acad Sci 1129:305–322
Mazzotti DR, Guindalini C, de Souza AAL, Sato JR, Santos-Silva R, Bittencourt LRA, Tufik S (2012) Adenosine deaminase polymorphism affects sleep EEG spectral power in a large epidemiological sample. Plos One 7: e44154
McKenna BS, Dickinson DL, Orff HJ, Drummond SPA (2007) The effects of one night of sleep deprivation on known-risk and ambiguous-risk decisions. J Sleep Res 16:245–252
Mikulincer M, Babkoff H, Caspy T, Sing H (1989) The effects of 72 hours of sleep loss on psychological variables. Br J Psychol 80:145–162
Mistlberger RE (2005) Circadian regulation of sleep in mammals: role of the suprachiasmatic nucleus. Brain Res Rev 49:429–454
Monk TH (1982) The arousal model of time of day effects in human-performance efficiency. Chronobiologia 9:49–54
Mu QW, Mishory A, Johnson KA, Nahas Z, Kozel FA, Yamanaka K, Bohning DE, George MS (2005) Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. Sleep 28:433–446
Ogilvie RD, Mcdonagh DM, Stone SN, Wilkinson RT (1988) Eye-movements and the detection of sleep onset. Psychophysiology 25:81–91
Pace-Schott EF, Hutcherson CA, Bemporad B, Morgan A, Kumar A, Hobson JA, Stickgold R (2009) Failure to find executive function deficits following one night's total sleep deprivation in university students under naturalistic conditions. Behav Sleep Med 7:136–163
Palchykova S, Winsky-Sommerer R, Shen HY, Boison D, Gerling A, Tobler I (2010) Manipulation of adenosine kinase affects sleep regulation in mice. J Neurosci 30:13157–13165
Pascual O, Casper KB, Kubera C, Zhang J, Revilla-Sanchez R, Sul JY, Takano H, Moss SJ, McCarthy K, Haydon PG (2005) Astrocytic purinergic signaling coordinates synaptic networks. Science 310:113–116
Pierard C, Liscia P, Philippin JN, Mons N, Lafon T, Chauveau F, Van Beers P, Drouet I, Serra A, Jouanin JC, Beracochea D (2007) Modafinil restores memory performance and neural activity impaired by sleep deprivation in mice. Pharmacol Biochem Behav 88:55–63
Porkka-Heiskanen T, Kalinchuk AV (2011) Adenosine, energy metabolism and sleep homeostasis. Sleep Med Rev 15:123–135
Porkka-Heiskanen T, Strecker RE, McCarley RW (2000) Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: an in vivo microdialysis study. Neuroscience 99:507–517
Rajaratnam SM, Arendt J (2001) Health in a 24-h society. Lancet 358:999–1005
Rétey JV, Adam M, Honegger E, Khatami R, Luhmann UFO, Jung HH, Berger W, Landolt H-P (2005) A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. Proc Natl Acad Sci USA 102:15676–15681
Rétey JV, Adam M, Gottselig JM, Khatami R, Dürr R, Achermann P, Landolt H-P (2006) Adenosinergic mechanisms contribute to individual differences in sleep-deprivation induced changes in neurobehavioral function and brain rhythmic activity. J Neurosci 26:10472–10479

Rétey JV, Adam M, Khatami R, Luhmann UFO, Jung HH, Berger W, Landolt H-P (2007) A genetic variation in the adenosine A_{2A} receptor gene (*ADORA2A*) contributes to individual sensitivity to caffeine effects on sleep. Clin Pharmacol Ther 81:692–698

Riksen NP, Franke B, van den Broek P, Naber M, Smits P, Rongen GA (2008) The 22G > A polymorphism in the adenosine deaminase gene impairs catalytic function but does not affect reactive hyperaemia in humans in vivo. Pharmacogenet Genomics 18:843–846

Roediger HL, Mcdermott KB (1995) Creating false memories: remembering words not presented in lists. J Exp Psychol Learn Mem Cogn 21:803–814

Roenneberg T, Wirz-Justice A, Merrow M (2003) Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 18:80–90

Rogers PJ, Hohoff C, Heatherley SV, Mullings EL, Maxfield PJ, Evershed RP, Deckert J, Nutt DJ (2010) Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. Neuropsychopharmacol 35:1973–1983

Rupp TL, Wesensten NJ, Newman R, Balkin TJ (2013) PER3 and ADORA2A polymorphisms impact neurobehavioral performance during sleep restriction. J Sleep Res 22:160–165

Scammell TE, Gerashchenko DY, Mochizuki T, McCarthy MT, Estabrooke IV, Sears CA, Saper CB, Urade Y, Hayaishi O (2001) An adenosine A2a agonist increases sleep and induces Fos in ventrolateral preoptic neurons. Neurosci 107:653–663

Schacter DL, Norman KA, Koutstaal W (1998) The cognitive neuroscience of constructive memory. Ann Rev Psychol 49:289–318

Schmidt C, Collette F, Cajochen C, Peigneux P (2007) A time to think: circadian rhythms in human cognition. Cogn Neuropsychol 24:755–789

Schmidt C, Collette F, Leclercq Y, Sterpenich V, Vandewalle G, Berthomier P, Berthomier C, Phillips C, Tinguely G, Darsaud A, Gais S, Schabus M, Desseilles M, Dang-Vu TT, Salmon E, Balteau E, Degueldre C, Luxen A, Maquet P, Cajochen C, Peigneux P (2009) Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area. Science 324:516–519

Schmidt C, Peigneux P, Cajochen C (2012) Age-related changes in sleep and circadian rhythms: impact on cognitive performance and underlying neuroanatomical networks. Front Neurol 3:118

Sebastiao AM, Ribeiro JA (2009) Adenosine receptors and the central nervous system. In: Wilson CN, Mustafa SJ (eds) Handbook of Experimental Pharmacology. Springer, Berlin, pp 471–534

Sherin JE, Shiromani PJ, McCarley RW, Saper CB (1996) Activation of ventrolateral preoptic neurons during sleep. Science 271:216–219

Steriade M, Timofeev I, Grenier F (2001) Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol 85:1969–1985

Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ, Rainnie DG, Portas CM, Greene RW, McCarley RW (2000) Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. Behav Brain Res 115:183–204

Strogatz SH, Kronauer RE, Czeisler CA (1987) Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia. Am J Physiol 253:R172–R178

Studer FE, Fedele DE, Marowsky A, Schwerdel C, Wernli K, Vogt K, Fritschy JM, Boison D (2006) Shift of adenosine kinase expression from neurons to astrocytes during postnatal development suggests dual functionality of the enzyme. Neuroscience 142:125–137

Taillard J, Philip P, Coste O, Sagaspe P, Bioulac B (2003) The circadian and homeostatic modulation of sleep pressure during wakefulness differs between morning and evening chronotypes. J Sleep Res 12:275–282

Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, Wagner H, Thorne D, Popp K, Rowland L, Welsh A, Balwinski S, Redmond D (2000) Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res 9:335–352

Timofeev I, Grenier F, Steriade M (2001) Disfacilitation and active inhibition in the neocortex during the natural sleep-wake cycle: an intracellular study. Proc Natl Acad Sci USA 98:1924–1929

Valdez P, Ramirez C, Garcia A, Talamantes J, Armijo P, Borrani J (2005) Circadian rhythms in components of attention. Biol Rhythm Res 36:57–65

Van Dongen HP, Price NJ, Mullington JM, Szuba MP, Kapoor SC, Dinges DF (2001) Caffeine eliminates psychomotor vigilance deficits from sleep inertia. Sleep 24:813–819

Van Dongen HP, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26:117–126

Van Dongen HPA, Baynard MD, Maislin G, Dinges DF (2004) Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. Sleep 27:423–433

Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li XY, Descalzi G, Kim SS, Chen T, Shang YZ, Zhuo M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signaling in the hippocampus. Nature 461:1122–1125

Venkatraman V, Chuah YML, Huettel SA, Chee MWL (2007) Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. Sleep 30:603–609

Venkatraman V, Huettel SA, Chuah LYM, Payne JW, Chee MWL (2011) Sleep deprivation biases the neural mechanisms underlying economic preferences. J Neurosci 31:3712–3718

Virus RM, Djuricic-Nedelson M, Radulovacki M, Green RD (1983) The effects of adenosine and 2′-deoxycoformycin on sleep and wakefulness in rats. Neuropharmacol 22:1401–1404

Walker MP (2008) Cognitive consequences of sleep and sleep loss. Sleep Med 9:S29–S34

Wyatt JK, Cajochen C, Ritz-De Cecco A, Czeisler CA, Dijk DJ (2004) Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. Sleep 27:374–381

Zaborszky L, Gaykema RP, Swanson DJ, Cullinan WE (1997) Cortical input to the basal forebrain. Neuroscience 79:1051–1078

Optogenetic Control of Hypocretin (Orexin) Neurons and Arousal Circuits

Luis de Lecea

Abstract In 1998, our group discovered a cDNA that encoded the precursor of two putative neuropeptides that we called hypocretins for their hypothalamic expression and their similarity to the secretin family of neuropeptides. In the last 16 years, numerous studies have placed the hypocretin system as an integrator of homeostatic functions with a crucial, non-redundant function as arousal stabilizer. We recently applied optogenetic methods to interrogate the role of individual neuronal circuits in sleep-to-wake transitions. The neuronal connections between the hypocretin system and the locus coeruleus (LC) seem to be crucial in establishing the appropriate dynamic of spontaneous awakenings.

Keywords Hypothalamus · Sleep/wake cycle · Neuropeptides · Narcolepsy · Awakenings · In vivo recordings · Knockout animals · Hypnotics

Contents

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1 Introduction

The term "arousal" usually refers to the degree of vigilance and alertness during wakefulness, manifesting as increased motor activation, responsiveness to sensory inputs, emotional reactivity, and enhanced cognitive processing.

The brain mechanisms underlying the organization of the sleep–wake cycle and general level of arousal remain unclear. The reticular activating system originally described by Moruzzi and Magoun originates in the brain stem and provides excitatory input to the cortex (Moruzzi and Magoun 1949). Activation of the reticular activating system, which includes fibers containing neuromodulators norepinephrine (NE), serotonin (5-HT), dopamine (DA), histamine (His), and acetylcholine (ACh), as well as fast transmitters (i.e., glutamate and GABA), has long been known to elicit an arousal-like state in decorticated cats (Steriade and McCarley 1990). Intracellular recordings in vivo by Steriade and colleagues showed that individual principal cortical neurons transition from irregular "up and down" states during NREM sleep, to regular firing patterns during wakefulness. McCormick and colleagues have shown that these transitions can be elicited in vitro by addition of a mixture of the neuromodulators mentioned above (Steriade et al. 1993). Also recently, Tafti and colleagues have shown that a similar cocktail of neurotransmitters and modulators can induce "desynchronization" of neuronal activity in neuronal cultures (Hinard et al. 2012). However, whether the neuronal components of the reticular activating system causally drive state transitions or merely correlate with cortical activity remained unclear.

Clearly, the neuronal circuits responsible for the transition from sleep to wakefulness need to be modulated and coordinated by multiple variables, including light, food, circadian rhythms, presence of a threat or predator, inflammation, or disease. The neurotransmitter hypocretin (Hcrt), also known as orexin (OX), appears to be a master integrator of these variables and critically modulates sleep-to-wake transitions (de Lecea et al. 1998; Sakurai et al. 1998). The hypocretin peptides, 28 and 33 amino acids in length, are derived from the same precursor and bind to 2G-protein-coupled receptors with different affinities. HcrtR1 (also known as OX1R) is expressed in deep layers of the cerebral cortex, hypothalamus, ventral tegmental area, and several brain stem nuclei, including a very prominent expression in the locus coeruleus (LC). In contrast, HcrtR2 (also known as OX2R) is expressed throughout the neocortex, septum, posterior hypothalamus, and raphe nuclei. Based on the fact that HcrtR-deficient dogs and mice are narcoleptic, but not mice with an HcrtR1 knockout allele, it appears that the two Hcrt receptors subserve different functions.

2 Hypocretins as Master Regulators of Arousal State Transitions

Hcrt-producing cells are constituted by a group $\sim$3,200 neurons in the mouse lateral hypothalamus ($\sim$6,700 and 50,000–80,000 in the rat and human brain, respectively) (Modirrousta et al. 2005). These neurons receive functional inputs from multiple

systems distributed in the cortex, limbic system, subcortical areas including the hypothalamus itself, thalamus, and ascending projections from the brain stem cholinergic nuclei, the reticular formation, the midbrain raphe nuclei, and the periaqueductal gray. In turn, these neurons project throughout the central nervous system, including to arousal and reward centers of the brain, to neurons expressing hcrt receptors. The afferent and efferent projections of hcrt neurons suggest that they play a role in multiple hypothalamic functions including regulating the sleep/wake cycle and goal-oriented behaviors. Interestingly, we have found that a specific efferent projection from hcrt neurons to noradrenergic LC neurons mediate sleep-to-wake transitions and possibly more general aspects of arousal.

Juxtacellular recordings of Hcrt neuron showed that they are generally quiescent during quiet wakefulness, SWS, and REM sleep but show high discharge rates during active wake and in anticipation of REM sleep-to-wake transitions (Lee et al. 2005; Mileykovskiy et al. 2005; Takahashi et al. 2008). In addition, they show high discharge rates during arousal elicited by environmental stimuli (e.g., an auditory stimulus and goal-oriented behavior) (Takahashi et al. 2008). These studies suggest that hcrt neurons participate in sleep-to-wake transitions, but cannot conclude whether the activity of Hcrt cells accompanies wakefulness or drives the transition.

Loss of function studies has clearly demonstrated the necessity of hcrt signaling for the integrity of behavioral states in mice, dogs, and humans (Sakurai 2007). This finding appeared to be of particular importance for our understanding of narcolepsy. Narcolepsy is a sleep disorder characterized by intrusions of sleep into wakefulness, as well as signs of dysregulated REM sleep and cataplexy, a sudden loss of muscle tone during wakefulness elicited by positive emotions. Narcoleptic patients with cataplexy have a complete absence of hcrt gene transcripts in the hypothalamus as well as non- or barely detectable levels of hcrt in the cerebrospinal fluid. Strong evidence supports that this is due to cell loss, as other markers that colocalize with Hcrt are also absent or significantly reduced in narcoleptic patients (e.g., dynorphin). Moreover, Mignot and colleagues also highlighted the importance of HcrtR2 in canine narcolepsy, as a breed of narcoleptic dogs displayed mutations in the HcrtR2 gene (Lin et al. 1999). Chemelli et al. (1999) demonstrated that a mutation of the Hcrt gene in mice resulted in behavioral arrests during the dark (active) period that resembled cataplexy-like attacks. Later studies have shown that HcrtR2 mutants also display these arrests, whereas HcrtR1 knockout mice do not show overt sleep abnormalities. Importantly, pharmacological or genetic rescue of hcrt gene expression alleviates narcolepsy symptoms in Hcrt-deficient mice (Mieda et al. 2004; Liu et al. 2011; Willie et al. 2011).

Intracerebroventricular (i.c.v.) infusion of hcrt peptides or hcrt agonists causes an increase in the time spent awake and a decrease in SWS and REM sleep [review in (Sakurai 2007)]. Stereotactic injection of the Hcrt-1 peptide in the LC, laterodorsal tegmentum, basal forebrain, or the lateral hypothalamus increased wakefulness and locomotor activity often associated with a marked reduction in SWS and REM sleep (Hagan et al. 1999). In vivo injection of Hcrt-1 in the LC resulted in dramatic changes in sleep architecture (Bourgin et al. 2000). More recently, genetic disinhibition of hcrt neurons using a selective GABA-B receptor gene deletion only in hcrt neurons induced severe fragmentation of sleep/wake states during both the light and dark

periods without showing an abnormality in total sleep/wake durations or signs of cataplexy (Matsuki et al. 2009). Collectively, these data suggest that the hcrt peptides are important to define boundaries between sleep and wake states, as shown by the fragmentation of sleep and wake state in animal models of narcolepsy.

The biological function of hcrt peptides is clearly necessary to maintain appropriate arousal and sleep. Studies in Hcrt receptor knockout mice seem to indicate that most of the effects of Hcrt on sleep are mediated through Hcrtr2 signaling. This is based on the fact that Hcrtr1 ko mice do not appear to have overt sleep abnormalities, whereas Hcrtr2 ko mice and dogs with mutations in Hcrtr2 show narcolepsy with cataplexy. The role of Hcrtr1 remains unclear because double Hcrtr1 and Hcrtr2 mutant mice show more episodes of behavioral arrests resembling cataplexy than single Hcrtr2 knockouts (Willie et al. 2003). It has been proposed that the control of wakefulness and NREM sleep to wake depends critically on Hcrtr2R (Mochizuki et al. 2011), while the dysregulation of REM sleep (unique to narcolepsy–cataplexy) results from the loss of signaling through both Hcrtr1R and Hcrt2R (Mieda et al. 2011). However, their implications in the regulation of narcolepsy, in particular cataplexy and sleep attack, remain unclear.

Importantly, activity in other arousal systems is strongly perturbed during cataplexy. LC neurons cease discharge and serotoninergic neurons significantly decrease their activity, while cells located in the amygdala (Gulyani et al. 2002) and the TMN showed an increased level of firing (John et al. 2004). This association suggests that both Hcrtr1 (LC, raphe) and Hcrtr2 (TMN, raphe) are involved in the maintenance of appropriate muscle tone. Recent studies also highlighted the role of altered cholinergic systems in triggering cataplexy in narcoleptic mice (Kalogiannis et al. 2010, 2011). Therefore, an important, unresolved goal is to identify the functional wiring of hcrt neurons, as well as the dynamics of synaptic release from hcrt terminals to precisely delineate the downstream projections (Li et al. 2014) that control arousal, sleep states, muscle tone, and goal-oriented behaviors.

Recordings in awake behaving animals show that LC neurons fire tonically at 1–3 Hz during awake states, fire less during SWS sleep, and are virtually silent during REM sleep (Berridge 2008). The LC also fires phasically in short bursts of 8–10 Hz during the presentation of salient stimuli that may increase wake duration. Like hcrt neurons, alterations in discharge rate precede changes in sleep-to-wake transitions (Aston-Jones and Bloom 1981a, b), suggesting that these cells are important for transitions to wakefulness or attention.

Interestingly, physical lesions of the LC do not elicit consistent changes in cortical EEG or behavioral indices of arousal (Cirelli et al. 1996). Genetic ablation of dopamine beta-hydroxylase, an enzyme required for NE synthesis, also does not disrupt sleep–wake states (Hunsley et al. 2006). This suggests the presence of redundant neural circuitry, external to the LC structure, supporting cortical activity and compensatory developmental mechanisms. However, central injections of pharmacological antagonists of α1- and β-noradrenergic receptors (Berridge and Espana 2000) have substantial sedative effects. Stimulation of neurons in the LC using local microinjections of a cholinergic agonist (bethanechol) produces rapid

activation of the forebrain EEG in halothane-anesthetized rats (Berridge and Foote 1991). Recently, the LC-NE system was shown to be critical for maintaining the increased membrane potential of cortical neurons in awake compared to sleep states (Constantinople and Bruno 2011). Taken together, these studies imply that the LC-NE system desynchronizes cortical activity and increases cortical membrane potential to increase arousal.

3 Optogenetic Dissection of hcrt and LC-NE Control of Arousal

We applied optogenetics to reversibly and selectively manipulate the activity of hcrt and LC neurons in freely moving animals (Adamantidis et al. 2007; Carter et al. 2009a, 2010, 2012; Carter and de Lecea 2011; Rolls et al. 2011). Optogenetics uses actuator opsin molecules (e.g., channelrhodopsin-2 (ChR2) or halorhodopsin-NpHR) to selectively activate or silence genetically targeted cells, with flashes of light at specific wavelength (Fig. 1).

Optogenetics provided the ideal tools to interrogate causal relationships between the activity of genetically identified neurons and brain states. Before optogenetics, it was difficult to selectively stimulate or inhibit specific hcrt and LC-NE populations with a temporal resolution relevant to sleep or wakefulness episodes and to achieve spatial selectivity to probe those cells without affecting surrounding cells or fibers of passage. This was particularly challenging in species where sleep and wakefulness are not consolidated such as laboratory rodents. Mice and rats have sleep cycles that last between 6 and 12 min and show frequent awakenings during the light (rest) cycle. This temporal scheme makes it impossible to use pharmacological interventions, as these span timescales that extend many sleep/wake cycles.

To deliver the optogenetic probes to hcrt or LC neurons, we used lentiviral and cre-dependent adeno-associated viral (AAV) gene delivery tools, under the control of cell-type specific (Adamantidis et al. 2007). To deliver light to the hcrt or LC field, we designed optical–neural interfaces in which optical fibers were chronically implanted on the mouse skull, as described elsewhere. Using this strategy, we were able to control hcrt neural activity both in vitro and in vivo with millisecond-precise optical stimulation (Adamantidis et al. 2007). The high temporal and spatial precision of stimulation allowed us to mimic the physiological range of hypocretin neuron discharge rates (1–30 Hz) (Hassani et al. 2009). Indeed, we used light-pulse trains for our optogenetic stimulation that were based on parameters on the actual frequency analysis of hcrt neurons in vivo (8–12 Hz). We found that direct unilateral optical stimulation of hcrt neurons increased the probability of transitions to wakefulness from either SWS or REM sleep. Interestingly, high-frequency optical stimulation (5–30 Hz light-pulse trains) reduced the latency to wakefulness, whereas 1 Hz trains did not, suggesting a frequency-dependent synaptic release of

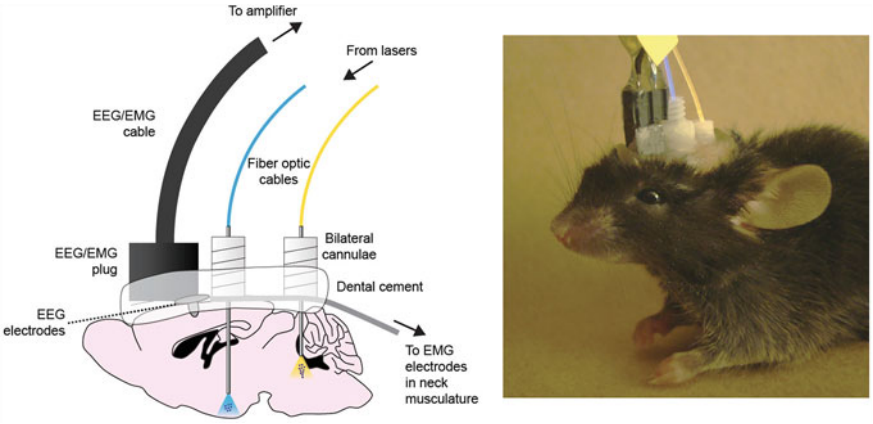

Fig. 1 Schematic of a mouse implanted with optical fibers connected with *blue* and *yellow* lasers for combinatorial optogenetic interrogations (Carter et al. 2012)

neurotransmitter (glutamate) and neuromodulators, including hcrt or dynorphin from the terminals. We further showed that the effects of stimulating hcrt neurons could be blocked by injection of an HcrtR antagonist or by genetic deletion of the hcrt gene, suggesting that hcrt peptides mediate, at least in part, optogenetically induced sleep-to-wake transitions and that fast transmission through glutamatergic terminals of Hcrt cells appears to be dispensable for Hcrt function. These experiments show that hcrt release from hcrt-expressing neurons is necessary for the wake-promoting properties of these neurons. It should be noted, however, that optogenetic stimulations may not reflect the actual patterns of activity in vivo, even if the frequencies are selected based on in vivo recordings. This is because it is unlikely that the volume of Hcrt cells stimulated by light will ever be activated synchronously. This was further supported by data showing that optical silencing of hcrt neurons promotes SWS (Tsunematsu et al. 2011, 2013).

These results were recently confirmed by Sasaki and collaborators (Sasaki et al. 2011), who used a chemogenetic approach called designer receptors exclusively activated by designer drugs (DREADDs) to activate and suppress hcrt neural activity. DREADD technology is based on the introduction of a mutated muscarinic receptor that is only activated in the presence of a synthetic ligand (clozapine N-oxide (CNO)). DREADDs allow bimodal modulation of neural activity with temporal resolution of several hours (Armbruster et al. 2007) and therefore is used as a complementary method of optogenetics in longer timescales. They found that activation of hcrt neural activity increased wakefulness, while suppression of hcrt activity promoted SWS.

We then showed that in sleep-deprived animals, optogenetic stimulation of Hcrt neurons failed to increase the probability of awakenings, suggesting that hcrt control of sleep–wake transitions is under the dependence of sleep homeostasis (Carter et al. 2009b). However, the effect of optogenetic stimulations of hcrt persisted in mice that are unable to synthesize histamine, suggesting that the histaminergic system is not

required for the effect of hcrt on sleep-to-wake transitions. This effect does not rule out a possible role of the Hcrt–TMN connection in other features of sleep dynamics, as evidenced by the rescue of sleepiness in narcoleptic mice when replacing Hcrtr2. Finally, we showed that downstream arousal centers such as the LC neurons increased their activity (as measured by c-Fos expression) in response to hcrt optogenetic stimulation. Because previous work showed an excitatory effect of hcrt on LC-NE neurons (Bourgin et al. 2000), we investigated the hcrt–LC connection and focused our experimental investigations on the noradrenergic LC as a new target for optogenetic manipulation.

In a follow-up study, we genetically targeted LC-NE neurons by stereotaxic injection of a Cre recombinase-dependent adeno-associated virus (rAAV) into knock-in mice selectively expressing Cre in tyrosine hydroxylase (TH) neuron (Carter et al. 2010). We found that both NpHR and ChR2 were functional and could inhibit and activate, respectively, LC-NE neurons both in vitro and in vivo. We found that optogenetic low-frequency (1–10 Hz) stimulation of LC-NE neurons caused immediate (<5 s) sleep-to-wake transitions from both SWS sleep and REM sleep. Detailed time/frequency analysis revealed that 20 pulses delivered over 5 s were sufficient to induce an awakening (Carter et al. 2010). Stimulation of LC neurons during wakefulness increased locomotor activity and the total time spent awake, confirming the strong arousal effect. LC-NE stimulation can be so robust as to wake an animal from isoflurane Hypnotics (Vazey and Aston-Jones 2014). In contrast, NpHR-mediated silencing of LC-NE neurons decreased the duration of wake episodes but did not block sleep-to-wake transitions when animals were asleep. Taken together, this study showed that activation of LC-NE neurons is necessary for maintaining normal durations of wakefulness (NpHR experiment) and sufficient to induce immediate sleep-to-wake transitions, sustained wakefulness, and increased locomotor arousal. Thus, we proposed that the LC-NE neurons act as a fast tuning system to promote sleep-to-wake transitions and general arousal. Interestingly, we found that sustained optical activation of LC-NE neurons induces locomotor arrest (Carter et al. 2010), an effect likely caused by the depletion of norepinephrine from LC terminals or overexcitation of downstream motor nuclei. Such behavioral arrests share common symptoms with cataplexy, catatonia, or behavioral freezing both in animal models of narcolepsy and in human patients (Scammell et al. 2009). Thus, we hypothesized that behavioral arrests in narcoleptic mice could be caused by the lack of inhibitory control of LC neurons, possibly exerted under normal conditions by GABAergic neurons sensitive to Hcrt (and likely expressing HcrtR2) in the peri-LC region.

Most recently, we tested the hypothesis that LC activity gates hcrt neuron's effects on sleep-to-wake transitions (Carter et al. 2012). We took a dual optogenetic approach to stimulate hcrt neurons while concomitantly inhibiting or stimulating noradrenergic LC neurons during SWS sleep. Silencing LC neurons during hcrt stimulation blocked hcrt-mediated sleep-to-wake transitions. To test whether an increase in LC excitability would facilitate Hcrt-induced awakenings, we used a variant channel rhodopsin known as step functional opsin (SFO). This channel can be activated by short pulses of blue light (1–10 ms) and can stay open up to 1 min, letting the flow of cations into the cell without necessarily reaching the

depolarization threshold. Thus, when an SFO was expressed in LC neurons and LC neurons were primed with a 10-ms pulse, Hcrt stimulation was much more effective at eliciting sleep-to-wake transitions (Carter et al. 2012). Taken together, our results show that the LC serves as a necessary and sufficient downstream effector for hcrt-mediated SWS-to-wake transitions during the inactive period.

4 Hcrt and LC-NE System Dynamics

Across our experimental studies, we observed that optogenetic manipulation of hcrt and LC-NE neurons affects sleep-to-wake transitions with dramatically different temporal dynamics (Adamantidis et al. 2010; Carter et al. 2009b, 2010, 2012). Acute optical activation of hcrt neurons causes sleep-to-wake transitions over a time period of 10–30 s, while stimulation of LC neurons causes sleep-to-wake transitions in less than 5 s. The delayed effect of Hcrt on transitions may be explained by in vitro recordings of laterodorsal tegmental neurons in response to Hcrt, which show maximal depolarizations 20–30 s after bath application of Hcrt. Another explanation was provided by a mathematical conductance-based model of Hcrt and LC neurons (Carter et al. 2012; de Lecea and Huerta 2014). According to this model, Hcrt would slowly depolarize LC neurons' subthreshold during a time window that is consistent with variable integration, that is, a "safety" window that would prevent spontaneous awakenings to irrelevant signals. If all conditions are met and the depolarization continues, then LC neurons produce spikes that may reach the awakening threshold.

One explanation is that hcrt neurons may act as an upstream integrator of arousal during hypothalamic-related functions, while the LC-NE system acts as a primary effector for arousal, stress, and attention (de Lecea and Huerta 2014). However, the neuronal effector systems are likely redundant and activated by distinct sets of inputs. Therefore, we cannot rule out that blocking other arousal systems, such as the central histaminergic and cholinergic systems, would also severely affect hcrt-induced behavioral state transitions in other experimental conditions.

Besides the short-term effects of photostimulation, it is of interest that experiments applying sustained $\sim$1–4-h photostimulation of hcrt neurons showed increased sleep-to-wake transitions without changing the total duration of wakefulness (Carter et al. 2009b; Rolls et al. 2011), whereas long-term photostimulation of LC-NE neurons significantly increased wakefulness duration (Carter et al. 2010). It thus seems that Hcrt neurons are very sensitive to sleep pressure and do not elicit awakenings efficiently in conditions of sleep deprivation. Interestingly, Muhlethaler and colleagues have observed that the sensitivity of Hcrt neurons to noradrenergic innervation depends on sleep pressure (Grivel et al. 2005). Together, these results suggest that the hcrt system may regulate sleep–wake boundaries, while LC-NE neurons may rather control wake duration by increasing cortical membrane potential and desynchronizing the cortical EEG. Also, interestingly, we showed that control of the boundaries between sleep states is crucial for the consolidation of long-term memory (Rolls et al. 2011).

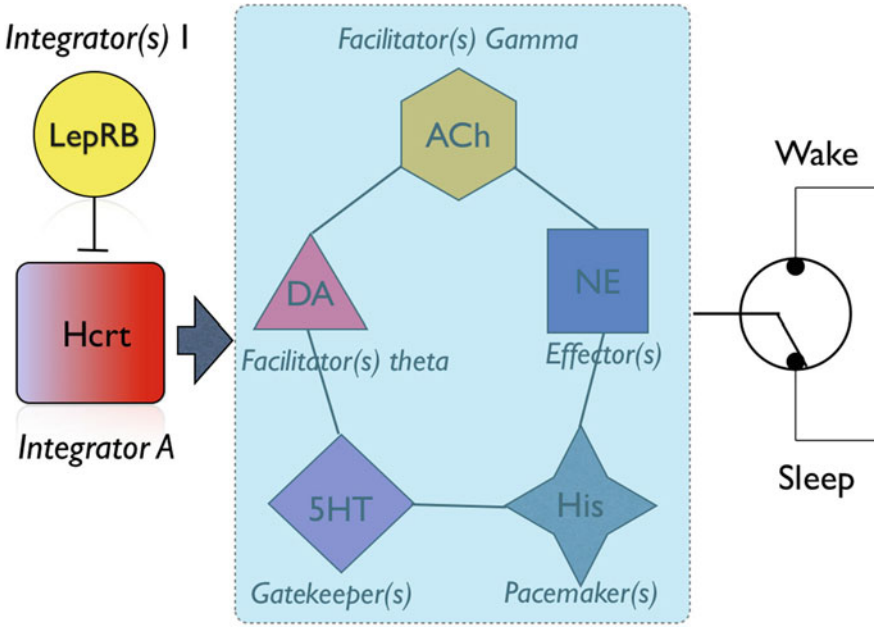

Fig. 2 Schematic of the interactions between Hcrt and arousal circuits. Hcrt neurons integrate information from metabolic, circadian, and limbic structures and convey the integrated information to a network of effectors, each of which has a different role in establishing the dynamic of a behavioral state transition

Obviously, the Hcrt–LC connection is not the only circuit involved in sleep-to-wake transitions. The role of histamine as a neuromodulator and powerful actor in sleep/wake cycles has long been documented. Anatomical studies revealed strong connectivity between lateral hypothalamic neurons and histaminergic cells in the tuberomammillary posterior hypothalamus. Trivedi et al. showed that His cells express Hcrtr2 (Trivedi et al. 1998). Moreover, Haas and colleagues demonstrated in slice experiments that His cells can be depolarized by Hcrt infusion (Eriksson et al. 2001). More recently, Burdakov and colleagues (Schone et al. 2014) have shown that optogenetic activation of Hcrtr2 is crucial for a reliable output of histaminergic neurons. These data, together with those of Mochizuki et al.'s discussed above, suggest an essential role of Hcrt-His circuitry in maintaining appropriate wakefulness. Thus, a picture is emerging in which the interaction of Hcrt with a network of neuromodulators defines the dynamic of sleep-to-wake transitions (Fig. 2). According to this scheme, Hcrt plays a fundamental role as a non-redundant neuromodulator of neuromodulators, providing the appropriate timescale of integration across multiple variables and transmitting this information into different timescales encoded by other transmitters such as norepinephrine, acetylcholine, or histamine.

5 Concluding Remarks

As optogenetics unravels the role of individual transmitters in sleep/wake dynamics, it may be possible to build a larger-scale framework predictive of sleep architecture based on the activity of ensembles of neurons. Such a framework could have important consequences on the treatment of sleep disorders and other neuropsychiatric conditions in which arousal state transitions are impaired.

References

Adamantidis AR, Zhang F, Aravanis AM et al (2007) Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 450:420–424

Adamantidis A, Carter MC, de Lecea L (2010) Optogenetic deconstruction of sleep-wake circuitry in the brain. Front Mol Neurosci 2:31

Armbruster BN, Li X, Pausch MH et al (2007) Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. In: Proceedings of the national academy of sciences of the United States of America, vol 104, pp 5163–5168

Aston-Jones G, Bloom FE (1981a) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1:876–886

Aston-Jones G, Bloom FE (1981b) Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. J Neurosci 1:887–900

Berridge CW (2008) Noradrenergic modulation of arousal. Brain Res Rev 58:1–17

Berridge CW, Espana RA (2000) Synergistic sedative effects of noradrenergic alpha(1)-and beta-receptor blockade on forebrain electroencephalographic and behavioral indices. Neuroscience 99:495–505

Berridge CW, Foote SL (1991) Effects of locus coeruleus activation on electroencephalographic activity in neocortex and hippocampus. J Neurosci 11:3135–3145

Bourgin P, Huitron-Resendiz S, Spier AD et al (2000) Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons. J Neurosci 20:7760–7765

Carter ME, de Lecea L (2011) Optogenetic investigation of neural circuits in vivo. Trends Mol Med 17:197–206

Carter ME, Borg JS, de Lecea L (2009a) The brain hypocretins and their receptors: mediators of allostatic arousal. Curr Opin Pharmacol 9:39–45

Carter ME, Adamantidis A, Ohtsu H et al (2009b) Sleep homeostasis modulates hypocretin-mediated sleep-to-wake transitions. J Neurosci 29:10939–10949

Carter ME, Yizhar O, Chikahisa S et al (2010) Tuning arousal with optogenetic modulation of locus coeruleus neurons. Nat Neurosci 13:1526–1533

Carter ME, Brill J, Bonnavion P et al (2012) Mechanism for hypocretin-mediated sleep-to-wake transitions. In: Proceedings of the national academy of sciences of the United States of America

Chemelli RM, Willie JT, Sinton CM et al (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98:437–451

Cirelli C, Pompeiano M, Tononi G (1996) Neuronal gene expression in the waking state: a role for the locus coeruleus. Science 274:1211–1215

Constantinople CM, Bruno RM (2011) Effects and mechanisms of wakefulness on local cortical networks. Neuron 69:1061–1068

de Lecea L, Huerta R (2014) Hypocretin (orexin) regulation of sleep-to-wake transitions. Front Pharmacol 5:16

de Lecea L, Kilduff TS, Peyron C et al (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. In: Proceedings of the national academy of sciences of the United States of America, vol 95 pp 322–327

Eriksson KS, Sergeeva O, Brown RE et al (2001) Orexin/hypocretin excites the histaminergic neurons of the tuberomammillary nucleus. J Neurosci 21:9273–9279

Grivel J, Cvetkovic V, Bayer L et al (2005) The wake-promoting hypocretin/orexin neurons change their response to noradrenaline after sleep deprivation. J Neurosci 25:4127–4130

Gulyani S, Wu MF, Nienhuis R et al (2002) Cataplexy-related neurons in the amygdala of the narcoleptic dog. Neuroscience 112:355–365

Hagan JJ, Leslie RA, Patel S et al (1999) Orexin A activates locus coeruleus cell firing and increases arousal in the rat. In: Proceedings of the national academy of sciences of the United States of America, vol 96, pp 10911–10916

Hassani OK, Lee MG, Jones BE (2009) Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. In: Proceedings of the national academy of sciences of the United States of America, vol 106, pp 2418–2422

Hinard V, Mikhail C, Pradervand S et al (2012) Key electrophysiological, molecular, and metabolic signatures of sleep and wakefulness revealed in primary cortical cultures. J Neurosci 32:12506–12517

Hunsley MS, Curtis WR, Palmiter RD (2006) Behavioral and sleep/wake characteristics of mice lacking norepinephrine and hypocretin. Genes Brain Behav 5:451–457

John J, Wu MF, Boehmer LN et al (2004) Cataplexy-active neurons in the hypothalamus: implications for the role of histamine in sleep and waking behavior. Neuron 42:619–634

Kalogiannis M, Grupke SL, Potter PE et al (2010) Narcoleptic orexin receptor knockout mice express enhanced cholinergic properties in laterodorsal tegmental neurons. Eur J Neurosci 32:130–142

Kalogiannis M, Hsu E, Willie JT et al (2011) Cholinergic modulation of narcoleptic attacks in double orexin receptor knockout mice. PLoS One 6:e18697

Lee MG, Hassani OK, Jones BE (2005) Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. J Neurosci 25:6716–6720

Li J, Hu Z, de Lecea L (2014) The hypocretins/orexins: integrators of multiple physiological functions. Br J Pharmacol 171:332–350

Lin L, Faraco J, Li R et al (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98:365–376

Liu M, Blanco-Centurion C, Konadhode R et al (2011) Orexin gene transfer into zona incerta neurons suppresses muscle paralysis in narcoleptic mice. J Neurosci 31:6028–6040

Matsuki T, Nomiyama M, Takahira H et al (2009) Selective loss of GABA(B) receptors in orexin-producing neurons results in disrupted sleep/wakefulness architecture. In: Proceedings of the national academy of sciences of the United States of America, vol 106, pp 4459–4464

Mieda M, Willie JT, Hara J et al (2004) Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice. In: Proceedings of the national academy of sciences of the United States of America, vol 101, pp 4649–4654

Mieda M, Hasegawa E, Kisanuki YY et al (2011) Differential roles of orexin receptor-1 and -2 in the regulation of non-REM and REM sleep. J Neurosci 31:6518–6526

Mileykovskiy BY, Kiyashchenko LI, Siegel JM (2005) Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 46:787–798

Mochizuki T, Arrigoni E, Marcus JN et al (2011) Orexin receptor 2 expression in the posterior hypothalamus rescues sleepiness in narcoleptic mice. In: Proceedings of the national academy of sciences of the United States of America, vol 108, pp 4471–4476

Modirrousta M, Mainville L, Jones BE (2005) Orexin and MCH neurons express c-Fos differently after sleep deprivation vs. recovery and bear different adrenergic receptors. Eur J Neurosci 21:2807–2816

Moruzzi G, Magoun HW (1949) Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1:455–473

Rolls A, Colas D, Adamantidis A et al (2011) Optogenetic disruption of sleep continuity impairs memory consolidation. In: Proceedings of the national academy of sciences of the United States of America, vol 108, pp 13305–13310

Sakurai T (2007) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci 8:171–181

Sakurai T, Amemiya A, Ishii M et al (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92:573–585

Sasaki K, Suzuki M, Mieda M et al (2011) Pharmacogenetic modulation of orexin neurons alters sleep/wakefulness states in mice. PLoS ONE 6:e20360

Scammell TE, Willie JT, Guilleminault C et al (2009) A consensus definition of cataplexy in mouse models of narcolepsy. Sleep 32:111–116

Schone C, Apergis-Schoute J, Sakurai T et al (2014) Coreleased orexin and glutamate evoke nonredundant spike outputs and computations in histamine neurons. Cell reports 7:697–704

Steriade M, McCarley R (1990) Brainstem control of wakefulness and sleep. Plenum, New York

Steriade M, McCormick DA, Sejnowski TJ (1993) Thalamocortical oscillations in the sleeping and aroused brain. Science 262:679–685

Takahashi K, Lin JS, Sakai K (2008) Neuronal activity of orexin and non-orexin waking-active neurons during wake-sleep states in the mouse. Neuroscience 153:860–870

Trivedi P, Yu H, MacNeil DJ et al (1998) Distribution of orexin receptor mRNA in the rat brain. FEBS Lett 438:71–75

Tsunematsu T, Kilduff TS, Boyden ES et al (2011) Acute optogenetic silencing of orexin/hypocretin neurons induces slow-wave sleep in mice. J Neurosci 31:10529–10539

Tsunematsu T, Tabuchi S, Tanaka KF et al (2013) Long-lasting silencing of orexin/hypocretin neurons using archaerhodopsin induces slow-wave sleep in mice. Behav Brain Res 255:64–74

Vazey EM, Aston-Jones G (2014) Designer receptor manipulations reveal a role of the locus coeruleus noradrenergic system in isoflurane general anesthesia. In: Proceedings of the national academy of sciences of the United States of America, vol 111, pp 3859–3864

Willie JT, Chemelli RM, Sinton CM et al (2003) Distinct narcolepsy syndromes in Orexin receptor-2 and Orexin null mice: molecular genetic dissection of Non-REM and REM sleep regulatory processes. Neuron 38:715–730

Willie JT, Takahira H, Shibahara M et al (2011) Ectopic overexpression of orexin alters sleep/wakefulness states and muscle tone regulation during REM sleep in mice. J Mol Neurosci 43:155–161

Stress, Arousal, and Sleep

Larry D. Sanford, Deborah Suchecki and Peter Meerlo

Abstract Stress is considered to be an important cause of disrupted sleep and insomnia. However, controlled and experimental studies in rodents indicate that effects of stress on sleep–wake regulation are complex and may strongly depend on the nature of the stressor. While most stressors are associated with at least a brief period of arousal and wakefulness, the subsequent amount and architecture of recovery sleep can vary dramatically across conditions even though classical markers of acute stress such as corticosterone are virtually the same. Sleep after stress appears to be highly influenced by situational variables including whether the stressor was controllable and/or predictable, whether the individual had the possibility to learn and adapt, and by the relative resilience and vulnerability of the individual experiencing stress. There are multiple brain regions and neurochemical systems linking stress and sleep, and the specific balance and interactions between these systems may ultimately determine the alterations in sleep–wake architecture. Factors that appear to play an important role in stress-induced wakefulness and sleep changes include various monominergic neurotransmitters, hypocretins, corticotropin releasing factor, and prolactin. In addition to the brain regions directly involved in stress responses such as the hypothalamus, the locus coeruleus, and the amygdala, differential effects of stressor controllability on behavior and sleep may be mediated by the medial prefrontal cortex. These various brain regions interact and influence each other and in turn affect the activity of sleep–wake controlling centers in the brain. Also, these regions likely play significant roles in memory processes and

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participate in the way stressful memories may affect arousal and sleep. Finally, stress-induced changes in sleep-architecture may affect sleep-related neuronal plasticity processes and thereby contribute to cognitive dysfunction and psychiatric disorders.

Keywords Stress · Controllability · Predictability · Vulnerability · Individual differences · Fear · Arousal · Sleep disturbance · Insomnia · Psychopathology

Contents

1 Introduction

Stress is generally viewed as a major cause of disrupted sleep. Traumatic life events often result in sleep disturbances that may include insomnia or subjective sleep problems (Lavie 2001) and the persistence of these disturbances may be predictive of the future development of emotional and cognitive disorders (Chang et al. 1997; Koren et al. 2002; Neckelmann et al. 2007). Understandably, given the practical and ethical concerns, few controlled and experimental studies on severe stress and its effect on subsequent sleep have been done in human subjects. As such, most of the available data on stress and sleep have come from studies in laboratory rodents (Pawlyk et al. 2008). Importantly, the large body of animal studies based on a wide variety of experimental stress models indicates that effects of stress on sleep may be far more complex than a simple and prolonged increase of wakefulness. The impact

of stress on sleep may vary with specific characteristics of a stressor (e.g., duration, intensity, controllability, and predictability) and with characteristics of the individual experiencing stress (e.g., individual stress coping strategies, relative resilience, and vulnerability). In addition, any stressful situation provides an opportunity for learning, and the success or failure of an organism in developing an adaptive coping strategy can influence post-stress sleep and behavior. Subsequently, evoking stress-related memories can impact sleep and behavior in much the same fashion as the original stress.

There are significant overlaps of the neural circuitry and neurochemistry underlying the stress response and that regulating arousal and sleep. Thus, it is not surprising that the interaction between stress and sleep is implicated in a variety of disease processes and psychiatric disorders. However, it is important to note that even significant stress can be experienced without producing permanent or pathological changes. The stress response engages the physiological and behavioral resources needed to cope with a challenge followed by a return to normalcy when the situation is resolved. Indeed, the purpose of the stress response is to restore homeostasis (Johnson et al. 1992; Chrousos 2009).

In this review, we will discuss the complex effects of stress on sleep, the stress parameters that appear to be important in determining post-stress sleep, and the neurochemical and neuroanatomical substrates important in regulating the relationship between stress and sleep. Lastly, we will discuss factors linking stress and sleep in the genesis of stress-related disorders.

2 Complex Effects of Stress on Sleep Architecture

Much of our knowledge of the relationship between stress and sleep is based on animal models, which allow for controlled studies on the consequences of both acute and chronic stress. A wide variety of experimental paradigms have been used to assess effects of acute stress on sleep, including social defeat stress (Meerlo et al. 1997, 2001a; Meerlo and Turek 2001), restraint or immobilization (Rampin et al. 1991; Meerlo et al. 2001b), footshocks (Smith 1995; Palma et al. 2000; Sanford et al. 2005), water immersion (Smith 1995), cold exposure (Palma et al. 2000; Tiba et al. 2004, 2008), ether exposure (Roky et al. 1995; Bodosi et al. 2000), cage changes (Tang et al. 2004, 2005b), exposure to novel environments (Tang et al. 2004, 2005b), and exposure to novel objects (Schiffelholz and Aldenhoff 2002; Tang et al. 2004, 2005b). Studies aimed at chronic stress are often based on repetition of a stressful stimulus [i.e., intermittent footshock: (Kant et al. 1995)] or alternating presentations of different noxious stimuli [i.e., tilted cage, wet cage, food deprivation, etc. (Cheeta et al. 1997; Gronli et al. 2004)] over a prolonged period of time.

Despite the obvious variation in the nature of the stimuli applied, their use in studies on stress is motivated by the assumption that these stimuli and conditions are, to some degree, aversive to the animals. In many cases this assumption is supported by data showing activation of the classical neuroendocrine stress

systems, i.e., the sympatho-adrenal axis and the hypothalamic-pituitary-adrenal (HPA) axis. Indeed the major similarity between these models in terms of stress appears to be an increase in the plasma levels of the stress hormones adrenaline and corticosterone, although one has to keep in mind that such elevations occur in response to virtually any kind of challenge and not exclusively to aversive stimuli (Koolhaas et al. 2011). Importantly, though the outcome in many studies on stress and sleep is discussed in terms of general stress effects, the experimental paradigms that are used may have stimulus-specific effects as well.

2.1 Effects of Acute Stress

Stress is generally considered to be a functional response of the brain and the body to challenges that humans and other animals may face. Coping with environmental challenges requires alertness and, since stress is a state of physiological activation and arousal, by definition, it inhibits sleep. Indeed, exposing animals to stressors is invariably associated with at least a short-lasting increase in wakefulness. Consistent with this aspect of the stress response, several of the classical neuropeptides and hormones involved in the stress response are known to promote wakefulness (see Sect. 4).

After the initial phase of arousal, sleep architecture is often altered; but in ways that may vary among stressors. In addition to inhibiting all sleep, some stressors may have a more pronounced and prolonged inhibiting effect on rapid eye movement (REM) sleep, that is, once the animals fall asleep there may be a prolonged period of time with non-REM (NREM) sleep but little or no REM sleep. This has been shown, for example, in rodents after exposure to severe social stress (Meerlo and Turek 2001) and exposure to multiple presentations of inescapable footshock stress (Adrien et al. 1991; Liu et al. 2003; Sanford et al. 2003a, b, c).

The initial period of stress-induced wakefulness and sleep disruption is most often followed by a rebound to compensate for the NREM and/or REM sleep that was lost. However, how much of the lost sleep is compensated and which sleep state varies widely between studies and stressors. For example, in rodents exposed to acute social stress, the initial loss of REM sleep is largely compensated during the subsequent recovery period (Meerlo and Turek 2001). However, such a REM sleep rebound may not occur after exposure to inescapable footshock stress in fear conditioning paradigms (Sanford et al. 2003a, b, c, 2010) or learned helplessness paradigms (Adrien et al. 1991).

Intriguingly, after some stressors, animals appear to gain more sleep than was actually lost during and immediately following the stress. For example, controlled studies in laboratory rats and mice showed that exposure to acute social stress, i.e., a 1 h interaction with an aggressive male conspecific, is followed by deeper or longer NREM sleep than a similar period of non-stressful sleep deprivation (Meerlo et al. 1997; Meerlo and Turek 2001). On the other hand, other studies have shown that acute immobilization or restraint stress is often followed by a

selective increase in REM sleep (Rampin et al. 1991; Meerlo et al. 2001b). The latter has long been the basis for the widely held belief that stress causes an increase in REM sleep, which we now know is clearly not a general feature of all stressors. It has not been established whether the stressor-specific increases in one sleep state or another reflect disturbances in sleep regulation or perhaps functional adaptations that evolved to deal with and recover from different stress conditions. Indeed, it has been argued that acute social stress may represent a form of intense wakefulness associated with increased brain activity, which would require a higher than normal need for recovery sleep (Meerlo et al. 1997). Similarly, the increase in REM sleep after e.g., immobilization stress has been suggested to be an adaptive coping response that may also serve the purpose of recovery (Suchecki et al. 2012). However, it remains unknown why some stressors are not followed by a complete compensation for the sleep that was lost, whereas other stressors are followed by more sleep than was lost. Nor is it understood why some stressors seem to promote NREM sleep whereas others are followed by an increase in REM sleep. This complex variation in the effects of different stressors on sleep may depend on the nature of the stressors and the specific effects they have on physiology and brain function. The variation in outcome may also be modulated by the way stressors are perceived by the individual, e.g., in terms of controllability and predictability see (Sects. 3.1 and 3.2), and whether or not a successful coping strategy is developed (Sect. 3.3).

Overall, the finding that, in most animal models of acute stress, the arousing and sleep-inhibiting effects of stressors are rapidly overcome and are sometimes followed by increased sleep during the recovery phase may seem at odds with the general notion that stress is a major cause of sleep disturbance and insomnia in humans. One explanation for this apparent inconsistency is that in laboratory rodents the physiological activation and arousal disappear quite rapidly upon termination of the stressor and return to the home cage, whereas human beings may carry their problems and stress with them. That is, the "stress" responsible for prolonged sleep disruption in humans may be a cognitive and emotional phenomenon that is not necessarily always associated with an acute challenge. Humans may suffer from stress based on memories of past events as well as worries and expectations about the future. In that respect, compared to some animals, the human brain may be more capable of turning a single acute stressor or life event that occurred in the past, or even one pending in the future, into a persistent and chronic stress state.

2.2 Repeated or Chronic Stress

With chronic stress, prolonged activation of the same behavioral, physiological, and metabolic processes beneficial for coping with an acute stressor can become detrimental (Chrousos 1998). Chronic stress has been reported to be a factor in the

disruption of sleep in a variety of situations including individuals lacking social support in the work environment (Gadinger et al. 2009; Nomura et al. 2009), children and adolescents exposed to traumatic events (Charuvastra and Cloitre 2009), and burnout patients (Armon et al. 2008). Chronic stress has also been viewed as a risk factor for the development of insomnia (Cartwright and Wood 1991).

A number of experimental studies in laboratory rats have applied a model of so-called chronic mild stress, which consists of exposing animals to a mixture of noxious stimuli, once or twice a day, for periods up to 3 or 4 weeks (e.g. Cheeta et al. 1997, Gronli et al. 2004). The stimuli include tilting of the cage, temporary exposure to a wet or soiled cage, food and water deprivation, exposure to prolonged periods of continuous lighting, and even stroboscopic lighting in one of the studies (Cheeta et al. 1997). The most significant finding in these studies was an increase in the amount of REM sleep the day after 3 or 4 weeks of treatment. The overall amount of sleep tended to be somewhat increased as well, which may in part reflect a rebound due to sleep loss during the actual stress exposure. Unfortunately, some of the stimuli applied, in particular the continuous or stroboscopic lighting, may have effects on sleep that have little to do with stress per se, for example through alterations in circadian function.

Chronic stress as discussed here partly relies on direct stimulation of the animals, which may explain some of the changes in sleep, whereas stress-related sleep disturbances in humans often appear to be of a more psychological nature. It may very well be that the physiological and neurobiological mechanisms resulting in disrupted sleep due to repeated presentations of actual stressors are quite different from those involved in psychological stress in humans. Although, these studies are important first steps toward developing relevant models for stress-related sleep disturbances and insomnia, perhaps research on the relationship between stress and sleep would gain by models that are based more on psychological factors; for instance, conditioned fear and arousal in which animals anticipate the occurrence of adverse events. Such an approach may have more resemblance with the psychological stress in humans, and may allow us to study central mechanisms by which sleep is disrupted and how such disturbances could best be treated.

3 Effects on Sleep May Vary with Specific Stress Parameters

While the importance of specific stress parameters and individual differences in stress sensitivity is generally well established, there has been very limited research on these issues with respect to their influence on sleep. Indeed, to date, much of the work on stress and sleep has been primarily descriptive and focused on effects of different types of stressors. The variable outcomes in terms of sleep

produced by different stressors clearly indicate that the observed changes are not simply a generalizable stress effect. One should thus be careful with the interpretation and extrapolation of findings from these types of studies and perhaps even not refer to the sleep changes as simple stress effects, as sleep after a stressful event can be modified as a consequence of specific stimuli or conditions. Indeed, in our view, experimental paradigms that manipulate specific stress parameters (e.g., duration, intensity, controllability, and predictability) and paradigms that consider organismal variables (e.g., learning and memory, resilience, and vulnerability) have considerably more potential for providing actual insight into the complex relationship between stress and sleep. In this section, we will provide an overview of how a number of these factors can modulate the stress-induced changes in sleep.

3.1 Stressor Controllability

Recent work has examined changes in sleep after controllable and uncontrollable stress, and of memories associated with each parameter, using a simple yoked control paradigm. In this paradigm, animals receive equal amounts of footshock, but one of the yoked pair can terminate the footshock simply by moving to the safe side of the shuttlebox. The actions of the yoked animal cannot alter shock presentation. Even though both animals receive equal shock, sleep in the post-shock period can be dramatically different. As demonstrated in Fig. 1, animals trained with controllable stress [escapable shock (ES)] can show significant enhancements of REM sleep, whereas their yoked controls that receive uncontrollable stress [inescapable shock (IS)] show significant reductions in REM sleep (Sanford et al. 2010). Returning the animals to the shock context without presenting footshock is also followed by increased REM in the controllable stress condition and decreased REM in the uncontrollable stress condition. Importantly, upon return to the shock context, both groups of mice show enhanced freezing, the primary behavioral indicator of fear memory (e.g. Blanchard and Blanchard 1969; Phillips and LeDoux 1992; Paylor et al. 1994). Training with ES and IS also elicits similar acute physiological stress responses as indicated by increased levels of plasma corticosterone (Shors et al. 1989) and increased body temperature (stress-induced hyperthermia) (Yang et al. 2011a). Thus, in this model, controllable and uncontrollable stress (and reminders of controllable and uncontrollable stress) result in similar activation of the acute stress response and behavioral indices of fear but directionally different alterations in REM. Controllability over a stressor does not simply dampen the changes in sleep but rather, it may result in qualitatively different changes. This work extends the findings based on the standard conditioned fear paradigm and further demonstrates that post-stress changes in sleep are not a simple function of the physical stress that an animal receives.

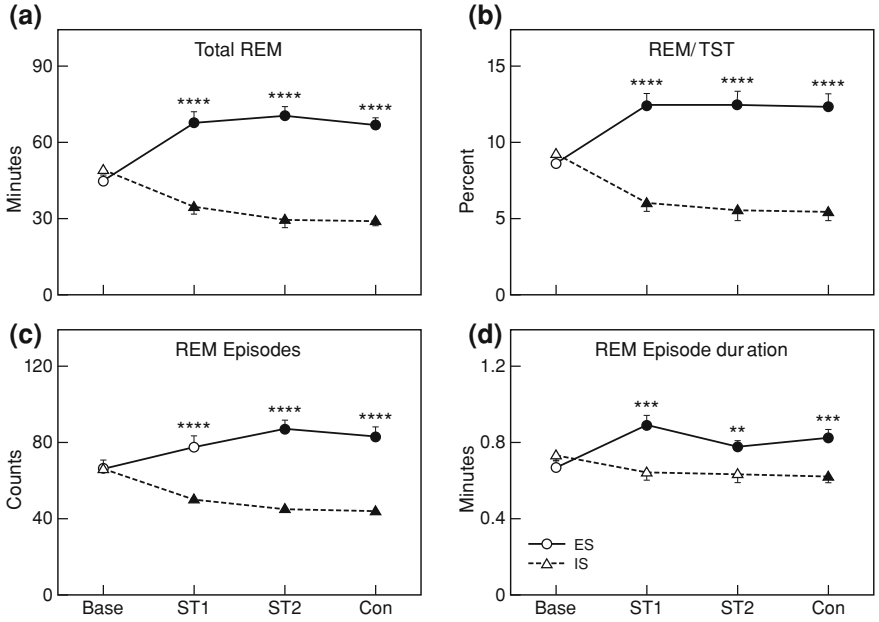

Fig. 1 REM sleep parameters plotted as 20 h totals for baseline (*Base*), two shock training days (*ST1*, *ST2*), and context (*Con*) in a study comparing the effects of controllable (modeled by escapable shock or ES) and uncontrollable (modeled by inescapable shock or IS) stress. **a** Total REM sleep. **b** REM sleep percentage (total REM sleep time/total sleep time). **c** Number of REM sleep episodes. **d** REM sleep episode duration. Significant differences between ES and IS: **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$ (Tukey test). Significant differences compared to Base (open symbols) are indicated by *dark circles* or *squares* for the ES and IS groups. Reprinted with permission from (Sanford et al. 2010)

3.2 Stressor Predictability

Predictability is an important factor in the effects of stress and a preference for predictability has been repeatedly demonstrated (French et al. 1972; Gliner 1972; Miller et al. 1974). For example, animals given the opportunity to determine whether shocks delivered to them will be signaled or unsignaled typically choose to spend their time in the signaled conditions regardless of whether the shock is escapable or inescapable [reviewed in (Badia et al. 1979)]. The strong behavioral effects suggest that predictability may also have a role in the modulating effects of stress on sleep. In fact, stressor predictability is a significant component in shock avoidance training in a shuttlebox, a paradigm in which laboratory rats are signaled of imminent shock and can learn to prevent shock from being delivered. Variants of this paradigm have often been used in studies of learning and sleep and have typically found increases in the amount of REM sleep at various latencies after training that have been interpreted as indicating a role for REM sleep in memory consolidation (e.g. Smith and Lapp 1986; Datta 2000). Unfortunately, the

potential role of predictability in modulating sleep after stress has received very little attention.

One study of stressor predictability in mice examined sleep after training with signaled escapable shock (SES) and signaled inescapable shock (SIS) (Yang et al. 2011a). Compared to mice experiencing SIS, those experiencing SES showed significantly increased REM sleep after each of two shock training sessions whereas compared to mice experiencing SES, those experiencing SIS showed significantly increased NREM sleep after both shock sessions. Interestingly, groups receiving either SES or SIS showed reduced REM sleep in response to cue presentation alone. In another study, mice exposed to either predictive or non-predictive auditory cues during training with ES also showed post-stress increases in REM sleep (Machida et al. 2013). However, a subgroup of mice (around 35 %) trained with the predictive auditory cue failed to improve their escape performance from the first to second day of training. Those mice that did not improve also did not show enhanced REM on either shock training day, suggesting a learning component in the alterations in REM sleep.

It is useful to compare these results to those obtained using non-signaled escapable and IS used to model controllable and uncontrollable stress as described above (Sanford et al. 2010). Without predictive cues, the relative differences in post-stress REM after escapable and IS were more pronounced. Contexts associated with non-signaled escapable and IS also produced directionally different changes in REM similar to those seen when shock was presented (Sanford et al. 2010), whereas predictive cues associated with either escapable or IS produced similar reductions in REM sleep.

While at this point the data are limited, these findings suggest that contexts and auditory cues associated with different shock training conditions may carry different, and potentially competing, types of information regarding the stressful situations. This difference is more pronounced in training with ESs as both contextual and cued fear associated with uncontrollable stress have similar effects on sleep in mice and both reduce REM (Sanford et al. 2003a, c). Thus, competing cued and contextual information associated with ESs may have interacted during training resulting in competing influences on REM, thereby suggesting that stressor predictability and controllability may interact in complex ways to modulate the changes in subsequent sleep.

3.3 Stress-Related Learning and Sleep

In addition to producing direct physiological effects, stressful situations provide an opportunity for learning as the individual responds to the stressor and seeks to use available information to cope with the ongoing challenge the stressor imposes. While in humans this could involve a variety of activities, including higher order cognitive processing; in rodents, the simplest behavioral responses to a stressor may be avoidance or escape attempts. In this case, stress-related parameters such

as controllability and predictability may provide useful information that shapes avoidance and escape behaviors thereby facilitating successful coping. By comparison, stressors that are uncontrollable or occur unpredictably do not provide information that can guide the animal to learn successful avoidance or escape behaviors. In these situations, the animal may still engage in escape attempts, but its behavior will not alter the presentation of the stressor or facilitate coping.

The impact of stressor controllability and predictability on behavior are central to a number of well-established learning paradigms that are motivated by stressful events. Of these, fear conditioning and related paradigms are beginning to demonstrate that the learning options an animal has in a stressful situation play a significant role in determining the impact of stress.

Experimental fear conditioning is a learning paradigm in which an animal makes an association between an uncontrollable stressor (usually footshock) and previously neutral cues (typically auditory) or contextual information (the test box and experimental room). Afterwards, presenting the fearful cues and contexts alone elicit physiological and behavioral fear responses similar to those produced by the initial uncontrollable stressor. Fear conditioned alterations in sleep are now also established though these can vary with the amount of training and with the strain of rats or mice that is studied. In agreement with the data in previous sections showing that uncontrollable footshocks reduce REM sleep, the primary and most consistent effect of extensive training with inescapable footshock is a marked reduction in REM sleep that occurs both after the shock training and after presentation of shock associated fearful cues and contexts (Sanford et al. 2003a, c; Tang et al. 2005d). This reduction in REM sleep has been reported across species and across strains (Sanford et al. 2001, 2003a, c) and can occur without the rebound or recovery REM sleep that has been reported for most stressors (Sanford et al. 2003a, c). Changes in NREM sleep in fear conditioning studies appear to be less consistent. Some studies have reported increases in (light) NREM sleep (Adrien et al. 1991), whereas others have shown strain-dependent reductions in NREM sleep after shock training and fearful contexts (Sanford et al. 2003a). There also may be relatively less NREM sleep EEG delta power (slow wave activity) in animals that show greater fear conditioned changes in sleep (Tang et al. 2006). Critically, these studies demonstrate that fear conditioned memories of stressful events can produce mostly the same changes in sleep as those produced by the stressful event itself and indicate the importance of learning in both the immediate and lasting effects that stress can have on sleep.

3.4 Fear Extinction and Sleep

Fear extinction is another important type of stress-related learning. While fear conditioning can be involved in the long term, negative effects of stress, it also can underlie adaptive behavior that occurs only so long as the fear-inducing stimulus is predictive of, or associated with, an aversive event (Kishimoto et al. 2000;

Pitman et al. 2001). Repeated presentation of a fearful cue or context without shock results in fear extinction, a type of new learning that inhibits subsequent fear behavior without erasing the original memory for fear conditioning (Bouton 2004). It is the failure of extinction that has been linked to stress-related psychopathology, particularly posttraumatic stress disorder (PTSD) (Myers and Davis 2007).

The processes that make fear behaviors resistant to extinction remain mostly unknown though there appears to be a relationship between fear extinction and post-training REM sleep. Post-training REM sleep deprivation has been reported to impair extinction (as indicated by freezing) for light cues (Silvestri 2005), but not for auditory cues (Fu et al. 2007) previously paired with shock. REM sleep-deprived rats did show greater spontaneous recovery of freezing on a second day with presentation of the fearful auditory cue alone. Neither of these studies found that post-training REM sleep deprivation significantly altered contextual fear extinction learning or spontaneous recovery of freezing on a second day of testing (Silvestri 2005; Fu et al. 2007). However, sleep (both NREM and REM) following extinction of contextual fear does return to normal, whereas rats that continued to show fear exhibited reductions in REM sleep (Wellman et al. 2008).

3.5 Stressor Resilience and Vulnerability to Sleep Disturbance

Genetic differences in vulnerability and resilience are recognized as important factors in the development of stress-related pathology. For example, approximately 20–30 % of individuals who experience traumatic events may develop PTSD whereas others do not appear to suffer significant long-lasting effects (Cohen et al. 2003; Kerns et al. 2004). Attempts to develop animal models that better represent individual differences in clinical populations have included the selection of low and high responders to stressors in outbred rat strains (Cohen et al. 2003; Kerns et al. 2004). There is also evidence that differences in vulnerability are a factor in the impact of stress on sleep, but the significance of individual differences has not been fully appreciated in either studies of stress or in studies of sleep in general (Irmis et al. 1971, 1974; Tang et al. 2007).

Some of the best evidence for the role in resilience and vulnerability in the impact of stress on sleep comes from studies comparing inbred strains of rodents, which are genetically identical within strain but which vary genetically and phenotypically across strain. Work in mice and rats has demonstrated that strains that exhibited greater anxiety-like behaviors in response to challenges in wakefulness exhibited correspondingly greater and longer duration alterations in sleep after training with IS and after fearful cues (Sanford et al. 2003c) and contexts (Sanford et al. 2003a) associated with IS. In general, vulnerable mouse strains (e.g., BALB/cJ mice compared to more resilient C57BL/6 J mice) also showed greater decreases in sleep after stressful situations with unlearned responses, including exposure to an

open field (Tang et al. 2004), cage change, and novel objects placed in the home cage (Tang et al. 2005b). Moreover, BALB/cJ mice also do not show a significant REM sleep increase during recovery from restraint stress, whereas C57BL/6 J mice do (Meerlo et al. 2001b).

In addition to genetic determinants of individual resilience and vulnerability, environmental factors and prior experiences with stress also play a major role in shaping future responses to stressful challenges. One such factor is neonatal stress that can be induced by disruptions of mother–infant relationship and that can have repercussions for adult behavior (Levine 2005) though the specific effects of maternal separation on sleep have varied across studies. For example, 3 h of maternal separation from postnatal days 2–14 in rats has been reported to increase both spontaneous baseline REM sleep and cold-stress-induced changes in REM sleep in males (Tiba et al. 2004) and females (Tiba et al. 2008). Similarly, neonatal rats maternally separated for 3 h and exposed to chronic mild stress as adults were reported to show longer sleep time, more episodes of REM sleep, and more episodes of NREM sleep transitioning to REM sleep (Mrdalj et al. 2013). By comparison, 6 h of neonatal maternal deprivation reduced the time spent in REM, without changes in NREM sleep when the rats attained adulthood (Feng et al. 2012). In addition to differences in experimental procedure, another important aspect that may differentiate these studies is the strain of rats used. While Feng and co-workers used Sprague-Dawley rats, the other studies used Wistar rats, which display more maternal behavior upon reunion with their litters (Lehmann and Feldon 2000), possibly buffering potential harmful effects of the separation procedure.

4 Stress Mediators as an Important Cause of Arousal and Sleep Disturbance

The regulation of sleep and arousal involves multiple neurotransmitter systems as well as excitatory and inhibitory amino acids, peptides, purines, and neuronal and non-neuronal humoral (i.e., cytokines and prostaglandins) modulators (Steiger and Holsboer 1997; Steiger et al. 1998; Jones 2005; Steiger 2007; Luppi 2010; Espana and Scammell 2011). Many of these same neurotransmitters and neuromodulators are also influenced by and/or mediate the effects of stress and are likely involved in the effects of stress on sleep. This section will briefly review some of the major neurochemical systems that link stress and sleep.

4.1 Hypocretin/Orexin

Hypocretin-1 and -2 are a set of neuropeptides that are derived from the same precursor gene and produced by neurons located in the lateral hypothalamus. The hypocretins are also called orexins as they were independently discovered by two

research groups in 1998 and separately named as hypocretins (de Lecea et al. 1998) or orexins (Sakurai et al. 1998). The hypocretin containing neurons have widespread projections throughout the brain and play a role in a variety of functions including autonomic control, neuroendocrine function, and feeding. Numerous studies have also linked hypocretin to the regulation of the sleep–wake cycle, particularly the induction and maintenance of wakefulness (Kilduff and Peyron 2000; Sutcliffe and de Lecea 2002). Indeed, the hypocretin system activates various well-known wake-active and arousal promoting centers in the brain, including the histaminergic tuberomammilary nucleus, the noradrenergic locus coeruleus (LC), the serotonergic dorsal raphe, and the cholinergic cell clusters in the brainstem and basal forebrain (Peyron et al. 1998b). Impaired hypocretin transmission is a core pathophysiological factor of narcolepsy, a disease characterized by uncontrollable onset of sleep (Nishino et al. 2000; Kornum et al. 2011).

Several lines of evidence indicate that hypocretins/orexins may also play a role in the behavioral arousal and neuroendocrine activation associated with stress (Winsky-Sommerer et al. 2005). A close and bidirectional relationship exists between the hypocretin system and the HPA axis. Hypocretins stimulate the activity of the HPA axis in a dose-dependent manner, an effect that seems to be mediated at the hypothalamic level (Kuru et al. 2000; Samson et al. 2002) but not at the adrenal level (Jaszberenyi et al. 2000). Under stressful conditions, a dual hypocretin-1/hypocretin-2 receptor antagonist does not interfere with corticosterone secretion but does reverse the immediate waking effect of novelty and social stressors (Steiner et al. 2013). In turn, hypothalamic corticotropin releasing hormone (CRH) containing neurons project directly to the lateral hypothalamus hypocretin containing neurons, where CRH1 and 2 receptors are abundantly expressed (Winsky-Sommerer et al. 2004). Indeed, studies in mice have shown that exposure to footshock and restraint stress causes an activation of the lateral hypothalamic hypocretin neurons, an effect that is mediated by CRH (Winsky-Sommerer et al. 2005).

4.2 Corticotropin Releasing Hormone

CRH is a major mediator of central nervous system responses to stressors (Koob and Bloom 1985; Heinrichs et al. 1995; Koob 1999). Intracerebroventricular (ICV) administration of CRH in rats produces many of the signs associated with anxiety in humans, including increased wakefulness (Ehlers et al. 1986; Marrosu et al. 1990; Chang and Opp 1998), altered locomotor activity, and an exaggerated startle response (Swerdlow et al. 1986; Heilig et al. 1994). By comparison, CRH antagonists attenuate behavioral responses to stress (e.g. Aloisi et al. 1999; Basso et al. 1999; Deak et al. 1999).

CRH may not only play an important role in stress-induced wakefulness and arousal, it may also be partly responsible for changes in sleep architecture during the subsequent recovery phase (Gonzalez and Valatx 1997). However, the few studies examining the role of CRH in stress-induced alterations in sleep have

yielded conflicting data. This is exemplified with the work on restraint stress-induced increases in REM sleep. The ICV administration of the broad CRH antagonist α-helical CRH9–41 prior to restraint stress prevents the subsequent increase in REM, but does not alter spontaneous REM, NREM, or wakefulness in non-stressed rats (Gonzalez and Valatx 1997). In contrast, other investigators found no effect of restraint stress applied at the beginning of the dark period on subsequent sleep, and also found no effect of the CRH antagonist, astressin, on sleep after restraint (Chang and Opp 2002). By comparison, restraint exposure at the onset of the light period increases wakefulness and decreases both NREM and REM, and ICV administration of astressin attenuates the increase in wakefulness over a 5 h-period immediately after the end of restraint but does not alter arousal during the period when restraint was applied (Chang and Opp 2002). There may have been differences in the procedures used for restraint [e.g., whether or not it was conducted in the home cage (Chang and Opp 2002)] that could have produced different results in these studies.

A recent study (Kimura et al. 2010) examined baseline and recovery sleep after sleep deprivation in conditional mouse mutants that overexpress CRH in the entire central nervous system or only in the forebrain, including limbic structures. In baseline recordings, homozygous mice with either global or forebrain over-expression of CRH showed increased REM compared to controls and both homozygous and heterozygous mice with global overexpression of CRH showed enhanced recovery REM sleep after 6 h sleep deprivation. However, repeated ICV administration of CRH during prolonged REM sleep deprivation in rats inhibits the expected REM rebound (Machado et al. 2010). Enhanced REM sleep recovery, but not NREM sleep recovery, was blocked by oral administration of the CRH receptor type 1 (CRHR1) antagonist, DMP696, 1 h prior to the end of sleep deprivation. Peripheral stress hormone levels were not elevated during baseline and did not differ across genotypes after sleep deprivation. The authors concluded that enhanced REM sleep in these mice was most likely induced through the activation of CRHR1. Consistent with this conclusion is a report that repeated administration of α-helical CRH9–41 in rats over 10 h of sleep deprivation also reduced the amount of REM sleep recovery (Gonzalez and Valatx 1998).

However, there is a separate line of research that demonstrates an inhibiting effect of CRH on REM sleep. Fear conditioning with IS, an uncontrollable stressor, and the presentation of fearful contexts and cues associated with IS are followed by significant reductions in REM that occur in the first few hours after exposure (Sanford et al. 2003a, c). In mice, ICV administration of CRH enhances the reduction in REM sleep following fearful contexts, whereas ICV administration of the non specific CRH antagonist, astressin, attenuates fear-induced reductions in REM (Yang et al. 2009). Training with ES, and reminders of ES, can produce significant enhancements in REM sleep (Sanford et al. 2010). Microinjections of either saline or astressin prior to training produce similar, significant enhancements in post-stress REM sleep relative to a non-shocked handling control condition, whereas the increases in REM sleep are blocked by pretreatment with CRH (Yang

et al. 2011b). The effect of CRH seems to be relatively specific for REM sleep as changes in NREM sleep and wakefulness were minimal. One potential explanation for differences across studies is that administration of a CRH antagonist simply blocked the initiation of neural processes that would have led to a subsequent increase in REM sleep.

4.3 Prolactin

A variety of studies have indicated that prolactin can promote REM sleep. Both systemic and ICV injection of prolactin enhances REM sleep in rats (Roky et al. 1995), whereas administration of a prolactin antiserum reduces the amount REM sleep without affecting NREM sleep (Obal et al. 1992). Also, the amount of REM sleep was found to be reduced in prolactin-deficient mice, which could be reversed by prolactin replacement (Obal et al. 2005).

Several studies in laboratory rodents have shown that the plasma level of prolactin increases in response to a wide variety of stressors, including restraint stress and ether exposure (Lenox et al. 1980; Meerlo et al. 2001b) suggesting that it may play a role in the effects of stress on sleep. A comparative study on different strains of mice showed that C57BL/6 J mice and BALB/cJ mice had similar corticosterone responses to restraint stress; however, the effects on prolactin and subsequent sleep were quite different. Restraint stress caused a concomitant increase in prolactin and REM sleep in the C57BL/6 J mice, but not in BALB/cJ mice, which supports the idea that prolactin might be involved in the mechanism underlying restraint stress-induced REM sleep (Meerlo et al. 2001b). Direct evidence for prolactin as a mediator of stress-related increases in REM sleep comes from a study in rats showing that an ether exposure-induced increase in REM sleep could be blocked by hypophysectomy and by ICV administration of an antiserum to prolactin (Bodosi et al. 2000). Other data implicating prolactin in stress-induced alterations in sleep come from a study examining post-stress sleep in REM sleep-deprived rats subsequently submitted to single or repeated sessions of footshock (Machado et al. 2008). REM sleep rebound was greater in the REM sleep-deprived rats that received multiple sessions of footshock, and the increase was associated with higher levels of prolactin (Machado et al. 2008).

Together these studies suggest that stressful stimuli and conditions that are associated with strong increases in prolactin levels may be followed by sleep with increased amounts of REM sleep. The precise mechanism of these effects of prolactin remains to be clarified but may involve a direct stimulatory effect of prolactin on cholinergic neurons in the mesopontine tegmental area involved in REM-sleep induction (Takahashi et al. 2000).

4.4 Monoamines

Serotonin (5-HT) containing neurons in the dorsal raphe nucleus (DRN), noradrenaline (NA) containing neurons in the LC, and histamine containing neurons in the tuberomammillary nucleus are wake-active and act directly on cortical and subcortical regions to promote wakefulness (Jones 2005). The 5-HT and NA systems are strongly stress-reactive (see discussion below) whereas there has been less work on the role of the histaminergic system. However, it is involved with the regulation of the stress response as central administration of histamine produces increases in adrenocorticotropin and corticosterone (Rudolph et al. 1979; Knigge and Warberg 1991) and blocking histamine synthesis or administration of antagonists block ACTH, beta-endorphin and prolactin responses to some stressors (Rudolph et al. 1979; Seltzer et al. 1986; Knigge and Warberg 1991; Kjaer et al. 1993; Fleckenstein et al. 1994). There also appears to be heterogeneity in specific histaminergic cells groups with respect to responding to different stressors (Miklos and Kovacs 2003).

Interestingly, each of these systems has been implicated in the enhancement of REM sleep that typically follows restraint stress. The increase is not found in 5-HT1A knockout mice (Boutrel et al. 2002; Popa et al. 2006) or in mice lacking the 5-HT transporter (Rachalski et al. 2009). Administration of the serotonin synthesis inhibitor para-chlorophenylalanine (Sinha 2006), neurotoxic destruction of noradrenergic cells in LC (Gonzalez et al. 1995), and administration of the histamine H1 receptor antagonist, chlorpheniramine, also prevent the increase in REM sleep induced by restraint in rats (Rojas-Zamorano et al. 2009). However, the actual cause of the attenuation of the REM sleep increase is not yet fully understood. As indicated for CRH, alterations in these systems prior to stress could simply alter the intensity of some elements of the stress response such that the processes that result in the post-restraint increase in REM sleep are not engaged.

5 Brain Regions Linking Stress, Arousal and Sleep

As discussed in the above section on stress mediators, there are several points of overlap in the neural regions/systems involved in stress and those directly involved in arousal. This section will focus on the amygdala and medial prefrontal cortex (mPFC), two regions not typically considered as direct regulators of arousal and sleep but which play significant roles in mediating the effects of stress on sleep and arousal (see Fig. 2).

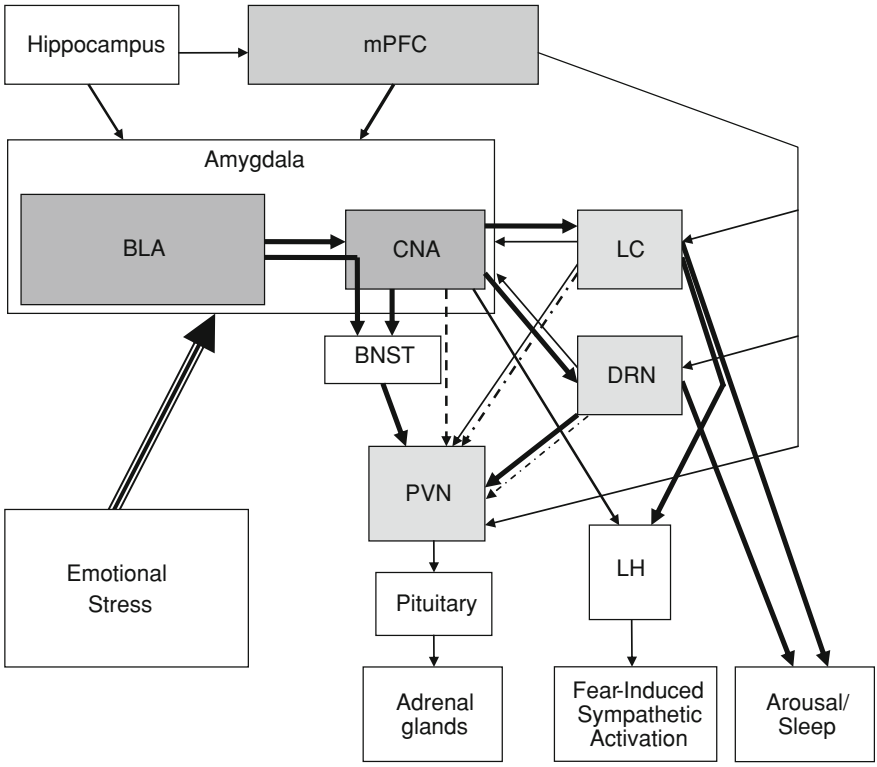

Fig. 2 This diagram illustrates the principal circuitry (*shaded*) that we are discussing in this section along with some of their connections to other regions involved in stress and sleep. In this figure, emotional stress would act on the amygdala which would be regulated by the hippocampus (contextual information) and the mPFC (perceived stressor control). BLA would act on CNA and the BNST to regulate the peripheral stress axis via PVN. Output from CNA would also impact LC and DRN, which have roles in regulating REM sleep and arousal as well as in regulating PVN. Both CNA and LC are involved in regulating fear-induced sympathetic activation via effects on LH. This diagram is necessarily incomplete, but illustrates the central role of the amygdala in controlling the stress axis, fear responses, and important components of the arousal system. *Heavyweight arrows* indicate presumed critical connections for mediating the effects of stress on sleep. *Lightweight arrows* indicate other connections that may play a role in regulating responses. *Dashed arrows* indicate indirect pathways. *BLA* basolateral nucleus of the amygdala, *BNST* bed nucleus of the stria terminalis, *CNA* central nucleus of the amygdala, *DRN* dorsal raphe nucleus, *LC* locus coeruleus, *LH* lateral hypothalamus, *mPFC* medial prefrontal cortex, *PVN* paraventricular nucleus

5.1 Amygdala and Stress-Induced Alterations in Arousal and Sleep

Several lines of research have demonstrated that the amygdala is a significant modulator of sleep. The majority of research on the role of the amygdala in regulating sleep has focused on its influence on REM sleep (e.g. Sanford et al. 1995,

1998, 2002; Calvo et al. 1996; Zhu et al. 1998;); however, a number of studies indicate that the amygdala can influence all sleep–wakefulness states (Sanford et al. 1995; 1998, 2006; Zhu et al. 1998). This influence most likely involves amygdalar projections to thalamic, hypothalamic, and brainstem target regions (Amaral et al. 1992) that are involved in the control of sleep and arousal. These include direct projections via the central nucleus of the amygdala [CNA; e.g. (Krettek and Price 1978; Inagaki et al. 1983; Price et al. 1987; Semba and Fibiger 1992; Peyron et al. 1998a)] and the lateral division of the bed nucleus of the stria terminalis [BNST; reviewed in (Amaral et al. 1992; Davis and Whalen 2001)], the source of the major descending outputs of the amygdala to brainstem regions linked to the regulation of REM sleep.

The amygdala is important in the regulation of behavioral, physiological, and neuroendocrine responses to stress (Roozendaal et al. 1991a, b; Bohus et al. 1996) and it appears to be a vital interface between stressful events and their impact on sleep and arousal. The BNST is an important relay for the influence of the amygdala on the hypothalamic paraventricular nucleus (PVN) (Forray and Gysling 2004), the final common pathway for information influencing the HPA axis (Pacak and Palkovits 2001; Herman et al. 2004) and a key site for integrating neuroendocrine, autonomic, and behavioral responses to stress (Chrousos 1998). GABA-ergic neurons in BNST can directly inhibit PVN and reduce ACTH secretion (Herman et al. 2004). By comparison, CNA has minimal direct projections to PVN (Prewitt and Herman 1998) and lesions of CNA do not directly influence PVN activation (Prewitt and Herman 1997) though CNA can influence PVN via trans-synaptic pathways through the dorsomedial hypothalamic nucleus and BNST (Prewitt and Herman 1998).

CNA does play a role in regulating the effects of stress on sleep, whereas a possible role for BNST has not been established. Inhibition of the CNA suppresses REM sleep whereas its activation [e.g., with electrical stimulation (Smith and Miskiman 1975)] can promote REM sleep in some situations. For example, functional inactivation of CNA with microinjections of the $GABA_A$ agonist, muscimol, produces a relatively selective decrease in REM sleep whereas blocking GABAergic inhibition with the $GABA_A$ antagonist, bicuculline, enhances REM sleep (Sanford et al. 2002). Functional lesions of the CNA by TTX, which inactivates both cell bodies and fibers of passage also decrease REM sleep and reduce arousal (Tang et al. 2005c). The decrease in REM sleep can occur without recovery (Tang et al. 2005c), a finding also reported for training with IS and fearful cues and contexts.

That stress-induced inactivation of CNA is involved in stress-induced reductions in REM sleep is also suggested by the lack of Fos activation in CNA after conditioned fear (Liu et al. 2003). Functionally, this hypothesis is supported by findings that bicuculline microinjected into CNA attenuates footshock-induced reductions in REM sleep whereas inactivation of CNA with muscimol did not (Liu et al. 2009). However, it should be noted that findings that activation of CNA promotes and inactivation of CNA reduces REM sleep appear at odds with the prevailing conventional view that CNA activation is responsible for regulating fear

responses via projections to the periaqueductal gray and other brainstem areas [Reviewed in (Duvarci et al. 2011)]. In fact, CNA neurons do fire in response to footshock stress (Rosenkranz et al. 2006) and in response to conditioned stimuli (Duvarci et al. 2011). However, CNA is inhibited by stimulation of the basal and lateral nuclei of the amygdala (Rosenkranz et al. 2006) both of which show high Fos expression after footshock (Liu et al. 2003). Thus, it is possible that CNA activation during fearful/stressful events does regulate fear behavior in wakefulness, but subsequently, with certain stressors, can be inhibited to decrease REM sleep in the post-stress period.

The involvement of the basolateral nucleus of the amygdala (BLA) in the control of sleep is indicated by reports that bilateral electrolytic and chemical lesions of BLA increase NREM sleep and total sleep time in rats (Zhu et al. 1998) and that bilateral chemical lesions of the amygdala produce more consolidated sleep in chair restrained Rhesus monkeys (Benca et al. 2000). Electrical and chemical stimulation of BLA also increase low voltage, high frequency activity in the cortical EEG and decrease NREM sleep and total sleep time, respectively (Dringenberg and Vanderwolf 1996; Zhu et al. 1998).

In general, the evidence suggests that CNA is more involved in the regulation of REM sleep than that of NREM sleep and that by comparison, BLA has a greater role in the regulation of NREM sleep and arousal. However, it is important to note that BLA regulates CNA output and therefore likely controls its influences on REM. Fibers from BLA also course through CNA on to the BNST which has brainstem targets similar to those of CNA (Davis and Whalen 2001), thereby providing an additional pathway by which BLA can influence brainstem regions. Indeed, it was recently found that microinjections into BLA of the Group II metabotropic glutamate (mGlu) receptor agonist, LY379268, selectively reduced REM sleep without significantly altering wakefulness or NREM sleep (Dong et al. 2012). By comparison, microinjection of LY379268 into CNA did not significantly alter sleep. Thus, group II mGlu receptors may influence specific cells in BLA that control descending outputs (possibly via CNA or BNST) that in turn regulate REM sleep generator regions in the brainstem.

The amygdala (including extended amygdala) is a critical region for the central effects of CRH, and it appears to mediate a number of the anxiogenic effects of CRH as evidenced by intra-amygdala microinjections of CRH agonists and antagonists [Reviewed in (Davis and Whalen 2001)]. For example, local application of CRH or urocortin (Sajdyk et al. 1999) into the BLA in rats produces dose-dependent increases in anxiety behaviors. CRH in the amygdala also plays a significant role in regulating stress-induced alterations in sleep.

It was reported that microinjections of the CRHR1 antagonist, antalarmin, into CNA in rats block fear-induced reductions in REM sleep and attenuate Fos expression in regions important in stress and REM sleep regulation including the PVN, LC, and DRN (Liu et al. 2011). Similarly, bilateral microinjections of antalarmin into BLA in rats do not alter spontaneous sleep, but do block the reduction in REM sleep produced by inescapable footshock (Wellman et al. 2013). Further, microinjecting antalarmin into BLA prior to shock training also blocked the

subsequent effects of contextual fear on REM sleep, but did not block fear memory or behavior as indicated by freezing. These data indicate that CRH receptors within the CNA and BLA are important in the regulation of stress- and fear-induced alterations in REM sleep, and also suggest that BLA plays a role in modulating how stressful memories influence sleep. The hippocampus is also likely to be involved. Information regarding fear conditioned contexts is first processed in the hippocampus and followed by BLA with output through CNA [reviewed in (LeDoux 2000)] and possibly BNST (Davis and Whalen 2001).

5.2 REM Regulatory Regions, Medial Prefrontal Cortex and Stressor Control

Stress often has a prominent effect on REM sleep (Sanford et al. 2003a, b, c; Jha et al. 2005). Thus, it is not surprising that brain regions directly implicated in the regulation REM sleep have significant roles in mediating the stress response. These include the LC and DRN. LC noradrenergic neurons and DRN serotonergic neurons are virtually silent during REM sleep and their activation may inhibit its generation (Steriade and McCarley 1990). LC and DRN also have connections to the PVN. PVN receives a large noradrenergic projection from brainstem A1 and A2 groups and a smaller projection from LC (Dunn et al. 2004). However, lesions of LC do reduce ACTH and corticosterone responses to acute stress (Ziegler et al. 1999), and there are suggestions that LC may impact PVN indirectly via limbic structures [reviewed in (Herman and Cullinan 1997)]. DRN has collateral serotonergic projections to CNA and PVN (Petrov et al. 1992, 1994), and 5-HT agonists enhance PVN activity as indicated by increased corticosterone levels and Fos expression (Mikkelsen et al. 2004). Indirect pathways may also play a role in serotonergic regulation of PVN (Herman and Cullinan 1997).

As discussed above, stressor controllability appears to be an important parameter in the effects of stress on sleep. Brainstem noradrenergic and serotonergic regions play important roles in stressor controllability. For example, IS in rats produced sustained increases in NA turnover in various brain regions regardless of stress duration, whereas with ES, NA utilization was reduced after rats had learned the coping response (Tsuda et al. 1987). IS also activates DRN serotonergic neurons to a greater degree than ES thereby increasing 5-HT in DRN and in target areas (Amat et al. 1998a, b; Hammack et al. 2002; Bland et al. 2003a, b). Administration of CRH into DRN produced behavioral changes like those seen with IS, whereas microinjection of a nonselective CRH antagonist blocked the behavioral changes normally seen with IS (Hammack et al. 2002, 2003a, b). The application of CRH to LC also increases NA release (Van Bockstaele et al. 1998).

The alterations in 5-HT and NA after inescapable and ES are consistent with their putative roles as inhibitory modulators of REM sleep and with the respective increases and decreases in REM sleep after controllable and uncontrollable stress. However, the evaluation of controllability requires assessment and evaluation of

information at the cortical level (Maier et al. 2006). The mPFC has been found to be a critical region in the perception of control and in mediating the consequences of stress (Maier et al. 2006; Smith and Vale 2006; Akirav and Maroun 2007). For example, blocking activation of the ventral mPFC with muscimol did not alter escape behavior in rats presented with IS, but blocking ventral mPFC in rats presented with ES produced failure in escape learning and greater fear conditioning (Maier et al. 2006). By comparison, activation of ventral mPFC with picrotoxin prior to IS promoted later escape learning in rats provided an opportunity to escape shock in a shuttlebox (Maier et al. 2006).

Unfortunately, the role of the mPFC in mediating the effects of stressor controllability on sleep has not been examined. However, part of the influence of mPFC is enacted through its effects on the DRN and possibly LC (Maier et al. 2006), providing a potential substrate for regulating alterations in REM sleep. For example, consistent with the discussion above, activation of mPFC inhibits DRN (Maier et al. 2006; Smith and Vale 2006). The prelimbic mPFC also has robust but restricted projections to the BLA and CNA, whereas the infralimbic mPFC projects to the medial, basomedial, cortical nuclei as well as to the CNA (Vertes 2004). There are projections from the mPFC to GABAergic neurons in the intercalated nuclei which have inhibitory control over CNA output, but there are conflicting reports regarding their specific origin within mPFC (see Vertes 2004). However, these projections from the mPFC to brainstem regulatory regions and the amygdala provide a substrate by which stressor controllability could influence REM sleep.

6 Stress, Sleep and Neuronal Plasticity: Implications for Stress-Related Disorders

Both NREM and REM sleep have putative roles in regulating neuronal plasticity and synaptic strength (Benington and Frank 2003; Tononi and Cirelli 2006; Meerlo et al. 2009; Havekes et al. 2012). Stress-induced changes in sleep and sleep architecture might lead to alterations in these plasticity processes and ultimately brain function. In fact, some of the changes in plasticity and brain function traditionally linked to stress may in part be related to alterations in sleep.

Work on stress and plasticity has distinguished the effects of acute and chronic stress. Acute stress can impact functional plasticity whereas chronic stress can differentially alter structural plasticity across brain regions. For example, chronic stress results in dendritic atrophy and reductions in spine density in the hippocampus (Magarinos and McEwen 1995a, b; Magarinos et al. 1997; Sandi et al. 2003; Stewart et al. 2005) and prefrontal cortex (Wellman 2001; Cook and Wellman 2004; Radley and Morrison 2005; Liston et al. 2006; Radley et al. 2006). Similar types of chronic stress produce increased dendritic arborization and increased spine density in BLA spiny neurons (Mitra et al. 2005; Vyas et al. 2006) and spine down-regulation in the medial amygdala (Bennur et al. 2007). Some stress-induced changes in the

hippocampus (Sandi et al. 2003; Stewart et al. 2005) and prefrontal cortex appear to be reversible whereas those in the amygdala are not [Reviewed in (Christoffel et al. 2011)]. Acute restraint, tail shock, and environmental stress impair long-term potentiation (LTP) in the hippocampus (Foy et al. 1987) and acute environmental stress can enhance long-term depression (Xu et al. 1997). However, stress-induced impairment in hippocampal LTP was significantly less in rats allowed to escape footshock than in yoked controls receiving identical shock, but not allowed to escape (Shors et al. 1989). This control mediated attenuation occurred even after a week of daily training sessions with relatively intense shock (30 trials, 1 mA, 1.5 s mean duration).

Although both sleep and stress can impact neuronal plasticity, their potential interactions in mediating alterations in plasticity have been minimally explored. The presence of interactions is indicated by the strong effects that stress can have on sleep as well as the demonstrated and hypothesized roles each has in mediating various aspects of plasticity. Importantly, post-stress sleep may have an adaptive function in coping with stress. This is suggested by the directionally different post-stress changes in REM sleep that occur following uncontrollable and controllable stress (Sanford et al. 2010) and the normalization in REM sleep that occurs following fear extinction versus the continued suppression of REM sleep in animals that still show fear (Wellman et al. 2008). These differences suggest that sleep and specific stress parameters may interact in mediating synaptic plasticity associated with stress-related learning and memory and/or the emotional valence of the memory. Indeed, a variety of authors have made suggestions consistent with this hypothesis, e.g., REM sleep functions to weaken unwanted memory traces in the cortex (Crick and Mitchison 1983); intact REM sleep aids in the processing of memory for trauma (Mellman et al. 2002, 2007); and REM sleep may play an important role in consolidating memories for aversive events and for "decoupling" those memories from their emotional charge (Nishida et al. 2009; Walker 2009).

Best et al. proposed that pyramidal neurons in the hippocampus change from a firing pattern that supports LTP in wakefulness to one that supports depotentiation during REM sleep; thereby putatively "resetting" the hippocampus after memories have been transferred to the frontal cortex and clearing the way for the formation of future memories (Best et al. 2007). If true, reductions in REM sleep induced by IS, particularly those that occur without recovery REM sleep (Sanford et al. 2003a, c), could impair this process. Impairment could also involve stress-induced enhancement of NA and 5-HT which facilitate LTP and may impede depotentiation [Reviewed in (Best et al. 2007)]. By comparison, enhancements of REM sleep and corresponding decreased activity in noradrenergic and serotonergic regions could facilitate the adaptive processing of strong memories. Post-stress NREM sleep may also be important. This is suggested by reports that rats trained with IS in an intense learned helplessness paradigm show increased light NREM sleep as well as decreased REM sleep (Adrien et al. 1991).

Sleep disturbances both before (Bryant et al. 2010) and after (Lavie 2001) traumatic events have been linked to the development of stress-related pathology. However, it is important to note that stress and the temporary alterations in sleep

associated with it typically do not give rise to persisting or detrimental effects. This suggests that being able to distinguish normal stress responses from those that can lead to pathology is likely key to fully understanding the processes leading to stress-related disorders. As stress-induced dysregulation of neuronal plasticity and remodeling of neural circuits are implicated in a variety of psychiatric disorders (McEwen 2007; Christoffel et al. 2011) understanding the role sleep plays in mediating the effects of stress on neuronal plasticity also may be critical for understanding how stress comes to produce persisting and pathological changes in the brain.

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References

Adrien J, Dugovic C, Martin P (1991) Sleep-wakefulness patterns in the helpless rat. Physiol Behav 49:257–262

Akirav I, Maroun M (2007). The role of the medial prefrontal cortex-amygdala circuit in stress effects on the extinction of fear. Neural Plast 2007: 30873

Aloisi AM, Bianchi M, Lupo C, Sacerdote P, Farabollini F (1999) Neuroendocrine and behavioral effects of CRH blockade and stress in male rats. Physiol Behav 66(3):523–528

Amaral D, Price J, Pitkanen A, Carmichael S (1992) Anatomical organization of the primate amygdaloid complex. In: Aggleton J (ed) The Amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. Wiley-Liss, Inc, New York, pp 1–66

Amat J, Matus-Amat P, Watkins LR, Maier SF (1998a) Escapable and inescapable stress differentially alter extracellular levels of 5-HT in the basolateral amygdala of the rat. Brain Res 812(1–2):113–120

Amat J, Matus-Amat P, Watkins LR, Maier SF (1998b) Escapable and inescapable stress differentially and selectively alter extracellular levels of 5-HT in the ventral hippocampus and dorsal periaqueductal gray of the rat. Brain Res 797(1):12–22

Armon G, Shirom A, Shapira I, Melamed S (2008) On the nature of burnout–insomnia relationships: a prospective study of employed adults. J Psychosom Res 65(1):5–12

Badia P, Harsh J, Abbott B (1979) Choosing between predictable and unpredictable shock conditions: data and theory. Psychol Bull 86(5):1107–1131

Basso AM, Spina M, Rivier J, Vale W, Koob GF (1999) Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. Psychopharmacology 145(1):21–30

Benca RM, Obermeyer WH, Shelton SE, Droster J, Kalin NH (2000) Effects of amygdala lesions on sleep in rhesus monkeys. Brain Res 879(1–2):130–138

Benington JH, Frank MG (2003) Cellular and molecular connections between sleep and synaptic plasticity. Prog Neurobiol 69(2):71–101

Bennur S, Shankaranarayana Rao BS, Pawlak R, Strickland S, McEwen BS, Chattarji S (2007) Stress-induced spine loss in the medial amygdala is mediated by tissue-plasminogen activator. Neuroscience 144(1):8–16

Best J, Diniz Behn C, Poe GR, Booth V (2007) Neuronal models for sleep–wake regulation and synaptic reorganization in the sleeping hippocampus. J Biol Rhythms 22(3):220–232

Blanchard RJ, Blanchard DC (1969) Crouching as an index of fear. J Comp Physiol Psychol 67(3):370–375
Bland ST, Hargrave D, Pepin JL, Amat J, Watkins LR, Maier SF (2003a) Stressor controllability modulates stress-induced dopamine and serotonin efflux and morphine-induced serotonin efflux in the medial prefrontal cortex. Neuropsychopharmacology 28:1589–1596
Bland ST, Twining C, Watkins LR, Maier SF (2003b) Stressor controllability modulates stress-induced serotonin but not dopamine efflux in the nucleus accumbens shell. Synapse 49(3):206–208
Bodosi B, Obal F Jr, Gardi J, Komlodi J, Fang J, Krueger JM (2000) An ether stressor increases REM sleep in rats: possible role of prolactin. Am J Physiol Regul Integr Comp Physiol 279(5):R1590–R1598
Bohus B, Koolhaas J, Luiten P, Korte S, Roozendaal B, Wiersma A (1996) The neurobiology of the central nucleus of the amygdala in relation to neuroendocrine outflow. Prog Brain Res 107:447–460
Bouton ME (2004) Context and behavioral processes in extinction. Learn Mem 11(5):485–494
Boutrel B, Monaca C, Hen R, Hamon M, Adrien J (2002) Involvement of 5-HT1A receptors in homeostatic and stress-induced adaptive regulations of paradoxical sleep: studies in 5-HT1A knock-out mice. J Neurosci 22(11):4686–4692
Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC (2010) Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. Sleep 33(1):69–74
Calvo J, Simón-Arceo K, Fernández-Mas R (1996) Prolonged enhancement of REM sleep produced by carbachol microinjection into the amygdala. NeuroRep 7:577–580
Cartwright RD, Wood E (1991) Adjustment disorders of sleep: the sleep effects of a major stressful event and its resolution. Psychiatry Res 39(3):199–209
Chang FC, Opp MR (1998) Blockade of corticotropin-releasing hormone receptors reduces spontaneous waking in the rat. Am J Physiol 275(3 Pt 2):R793–R802
Chang FC, Opp MR (2002) Role of corticotropin-releasing hormone in stressor-induced alterations of sleep in rat. Am J Physiol Regul Integr Comp Physiol 283(2):R400–R407
Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ (1997) Insomnia in young men and subsequent depression. The Johns Hopkins precursors study. Am J Epidemiol 146(2):105–114
Charuvastra A, Cloitre M (2009) Safe enough to sleep: sleep disruptions associated with trauma, posttraumatic stress, and anxiety in children and adolescents. Child Adolesc Psychiatr Clin N Am 18(4):877–891
Cheeta S, Ruigt G, van Proosdij J, Willner P (1997) Changes in sleep architecture following chronic mild stress. Biol Psychiatry 41(4):419–427
Christoffel DJ, Golden SA, Russo SJ (2011) Structural and synaptic plasticity in stress-related disorders. Rev Neurosci 22(5):535–549
Chrousos GP (1998) Stressors, stress, and neuroendocrine integration of the adaptive response. Ann N Y Acad Sci 851:311–335
Chrousos GP (2009) Stress and disorders of the stress system. Nature Rev Endocrinol 5(7):374–381
Cohen H, Zohar J, Matar M (2003) The relevance of differential response to trauma in an animal model of posttraumatic stress disorder. Biol Psychiatry 53(6):463–473
Cook SC, Wellman CL (2004) Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J Neurobiol 60(2):236–248
Crick F, Mitchison G (1983) The function of dream sleep. Nature 304(5922):111–114
Datta S (2000) Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. J Neurosci 20(22):8607–8613
Davis M, Whalen PJ (2001) The amygdala: vigilance and emotion. Mol Psychiatry 6(1):13–34
de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS 2nd, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 95(1):322–327

Deak T, Nguyen KT, Ehrlich AL, Watkins LR, Spencer RL, Maier SF, Licinio J, Wong ML, Chrousos GP, Webster E, Gold PW (1999) The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79–86

Dong E, Wellman LL, Yang L, Sanford LD (2012) Group II metabotropic glutamate receptors in the basal amygdala regulate rapid eye movement sleep. Brain Res 1452:85–95

Dringenberg HC, Vanderwolf CH (1996) Cholinergic activation of the electrocorticogram: an amygdaloid activating system. Exp Brain Res 108(2):285–296

Dunn AJ, Swiergiel AH, Palamarchouk V (2004) Brain circuits involved in corticotropin-releasing factor-norepinephrine interactions during stress. Ann N Y Acad Sci 1018:25–34

Duvarci S, Popa D, Pare D (2011) Central amygdala activity during fear conditioning. J Neurosci 31(1):289–294

Ehlers CL, Reed TK, Henriksen SJ (1986) Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. Neuroendocrinology 42(6):467–474

Espana RA, Scammell TE (2011) Sleep neurobiology from a clinical perspective. Sleep 34(7):845–858

Feng P, Hu Y, Vurbic D, Guo Y (2012) Maternal stress induces adult reduced REM sleep and melatonin level. Dev Neurobiol 72(5):677–687

Fleckenstein AE, Lookingland KJ, Moore KE (1994) Histaminergic neurons mediate restraint stress-induced increases in the activity of noradrenergic neurons projecting to the hypothalamus. Brain Res 653(1–2):273–277

Forray MI, Gysling K (2004) Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. Brain Res Rev 47(1–3):145–160

Foy MR, Stanton ME, Levine S, Thompson RF (1987) Behavioral stress impairs long-term potentiation in rodent hippocampus. Behav Neural Biol 48(1):138–149

French D, Palestine D, Leeb C (1972) Preference for a warning in an unavoidable shock situation: replication and extension. Psychol Rep 30:72–74

Fu J, Li P, Ouyang X, Gu C, Song Z, Gao J, Han L, Feng S, Tian S, Hu B (2007) Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats. Neuroscience 144(4):1186–1192

Gadinger MC, Fischer JE, Schneider S, Fischer GC, Frank G, Kromm W (2009) Female executives are particularly prone to the sleep-disturbing effect of isolated high-strain jobs: a cross-sectional study in German-speaking executives. J Sleep Res 18(2):229–237

Gliner JA (1972) Predictable versus unpredictable shock: preference behavior and stomach ulceration. Physiol Behav 9(5):693–698

Gonzalez MM, Valatx JL (1997) Effect of intracerebroventricular administration of alpha-helical CRH (9–41) on the sleep/waking cycle in rats under normal conditions or after subjection to an acute stressful stimulus. J Sleep Res 6(3):164–170

Gonzalez MM, Valatx JL (1998) Involvement of stress in the sleep rebound mechanism induced by sleep deprivation in the rat: use of alpha-helical CRH (9–41). Behav Pharmacol 9(8):655–662

Gonzalez MM, Debilly G, Valatx JL, Jouvet M (1995) Sleep increase after immobilization stress: role of the noradrenergic locus coeruleus system in the rat. Neurosci Lett 202(1–2):5–8

Gronli J, Murison R, Bjorvatn B, Sorensen E, Portas CM, Ursin R (2004) Chronic mild stress affects sucrose intake and sleep in rats. Behav Brain Res 150(1–2):139–147

Hammack SE, Richey KJ, Schmid MJ, LoPresti ML, Watkins LR, Maier SF (2002) The role of corticotropin-releasing hormone in the dorsal raphe nucleus in mediating the behavioral consequences of uncontrollable stress. J Neurosci 22(3):1020–1026

Hammack SE, Pepin JL, DesMarteau JS, Watkins LR, Maier SF (2003a) Low doses of corticotropin-releasing hormone injected into the dorsal raphe nucleus block the behavioral consequences of uncontrollable stress. Behav Brain Res 147(1–2):55–64

Hammack SE, Schmid MJ, LoPresti ML, Der-Avakian A, Pellymounter MA, Foster AC, Watkins LR, Maier SF (2003b) Corticotropin releasing hormone type 2 receptors in the dorsal

raphe nucleus mediate the behavioral consequences of uncontrollable stress. J Neurosci 23(3):1019–1025
Havekes R, Vecsey CG, Abel T (2012) The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. Cell Signal 24(6): 1251–1260
Heilig M, Koob G, Ekman R, Britton K (1994) Corticotropin-releasing factor and neuropeptide Y: role in emotional integration. Trends Neurosci 17:80–85
Heinrichs SC, Menzaghi F, Merlo Pich E, Britton KT, Koob GF (1995) The role of CRF in behavioral aspects of stress. Ann N Y Acad Sci 771:92–104
Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 20(2):78–84
Herman JP, Mueller NK, Figueiredo H (2004) Role of GABA and glutamate circuitry in hypothalamo-pituitary-adrenocortical stress integration. Ann N Y Acad Sci 1018:35–45
Inagaki S, Kawai Y, Matsuzaki T, Shiosaka S, Tohyama M (1983) Precise terminal fields of the descending somatostatinergic neuron system from the amygdaloid complex of the rat. J Hirnforsch 24(3):345–356
Irmis F, Lâat J, Radil-Weiss T (1971) Individual differences in hippocampal EEG during rhombencephalic sleep and arousal. Physiol Behav 7(1):117–119
Irmis F, Lâat J, Radil-Weiss T (1974) Individual (constitutional) differences in sleep patterns in rats. Behav Res Therapy 12:245–249
Jaszberenyi M, Bujdoso E, Pataki I, Telegdy G (2000) Effects of orexins on the hypothalamic-pituitary-adrenal system. J Neuroendocrinol 12(12):1174–1178
Jha SK, Brennan FX, Pawlyk AC, Ross RJ, Morrison AR (2005) REM sleep: a sensitive index of fear conditioning in rats. Eur J Neurosci 21(4):1077–1080
Johnson EO, Kamilaris TC, Chrousos GP, Gold PW (1992) Mechanisms of stress: a dynamic overview of hormonal and behavioral homeostasis. Neurosci Biobehav Rev 16(2):115–130
Jones BE (2005) From waking to sleeping: neuronal and chemical substrates. Trends Pharmacol Sci 26(11):578–586
Kant GJ, Pastel RH, Bauman RA, Meininger GR, Maughan KR, Robinson TN 3rd, Wright WL, Covington PS (1995) Effects of chronic stress on sleep in rats. Physiol Behav 57(2):359–365
Kerns JG, Cohen JD, MacDonald AW 3rd, Cho RY, Stenger VA, Carter CS (2004) Anterior cingulate conflict monitoring and adjustments in control. Science 303(5660):1023–1026
Kilduff TS, Peyron C (2000) The hypocretin/orexin ligand-receptor system: implications for sleep and sleep disorders. Trends Neurosci 23(8):359–365
Kimura M, Muller-Preuss P, Lu A, Wiesner E, Flachskamm C, Wurst W, Holsboer F, Deussing JM (2010) Conditional corticotropin-releasing hormone overexpression in the mouse forebrain enhances rapid eye movement sleep. Mol Psychiatry 15(2):154–165
Kishimoto T, Radulovic J, Radulovic M, Lin CR, Schrick C, Hooshmand F, Hermanson O, Rosenfeld MG, Spiess J (2000) Deletion of CRHR2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2. Nat Genet 24(4):415–419
Kjaer A, Knigge U, Madsen EL, Soe-Jensen P, Bach FW, Warberg J (1993) Insulin/hypoglycemia-induced adrenocorticotropin and beta-endorphin release: involvement of hypothalamic histaminergic neurons. Endocrinology 132(5):2213–2220
Knigge U, Warberg J (1991) The role of histamine in the neuroendocrine regulation of pituitary hormone secretion. Acta Endocrinol 124(6):609–619
Koob GF (1999) Corticotropin-releasing factor, norepinephrine, and stress. Biol Psychiatry 46(9):1167–1180
Koob G, Bloom F (1985) Corticotropin-releasing factor and behavior. Fed Proc 44:259–263
Koolhaas JM, Bartolomucci A, Buwalda B, de Boer SF, Flugge G, Korte SM, Meerlo P, Murison R, Olivier B, Palanza P, Richter-Levin G, Sgoifo A, Steimer T, Stiedl O, van Dijk G, Wohr M, Fuchs E (2011) Stress revisited: a critical evaluation of the stress concept. Neurosci Biobehav Rev 35(5):1291–1301

Koren D, Arnon I, Lavie P, Klein E (2002) Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. Am J Psychiatry 159:855–857

Kornum BR, Faraco J, Mignot E (2011) Narcolepsy with hypocretin/orexin deficiency, infections and autoimmunity of the brain. Curr Opin Neurobiol 21(6):897–903

Krettek JE, Price JL (1978) Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. J Comp Neurol 178(2):225–254

Kuru M, Ueta Y, Serino R, Nakazato M, Yamamoto Y, Shibuya I, Yamashita H (2000) Centrally administered orexin/hypocretin activates HPA axis in rats. NeuroReport 11(9):1977–1980

Lavie P (2001) Sleep disturbances in the wake of traumatic events. N Engl J Med 345:1825–1832

LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23:155–184

Lehmann J, Feldon J (2000) Long-term biobehavioral effects of maternal separation in the rat: consistent or confusing? Rev Neurosci 11(4):383–408

Lenox RH, Kant GJ, Sessions GR, Pennington LL, Mougey EH, Meyerhoff JL (1980) Specific hormonal and neurochemical responses to different stressors. Neuroendocrinology 30(5):300–308

Levine S (2005) Developmental determinants of sensitivity and resistance to stress. Psychoneuroendocrinology 30(10):939–946

Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS (2006) Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci 26(30):7870–7874

Liu X, Tang X, Sanford LD (2003) Fear-conditioned suppression of REM sleep: relationship to Fos expression patterns in limbic and brainstem regions in BALB/cJ mice. Brain Res 991(1–2):1–17

Liu X, Yang L, Wellman LL, Tang X, Sanford LD (2009) GABAergic antagonism of the central nucleus of the amygdala attenuates reductions in rapid eye movement sleep after inescapable footshock stress. Sleep 32(7):888–896

Liu X, Wellman LL, Yang L, Ambrozewicz MA, Tang X, Sanford LD (2011) Antagonizing corticotropin-releasing factor in the central nucleus of the amygdala attenuates fear-induced reductions in sleep but not freezing. Sleep 34(11):1539–1549

Luppi PH (2010) Neurochemical aspects of sleep regulation with specific focus on slow-wave sleep. World J Biol Psychiatry 11(Suppl 1):4–8

Machado RB, Tufik S, Suchecki D (2008) Chronic stress during paradoxical sleep deprivation increases paradoxical sleep rebound: association with prolactin plasma levels and brain serotonin content. Psychoneuroendocrinology 33(9):1211–1224

Machado RB, Tufik S, Suchecki D (2010) Modulation of Sleep Homeostasis by Corticotropin Releasing Hormone in REM Sleep-Deprived Rats. Int J Endocrinol 2010:326151

Machida M, Yang L, Wellman LL, Sanford LD (2013) Effects of stressor predictability on escape learning and sleep in mice. Sleep 36:421–430

Magarinos AM, McEwen BS (1995a) Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors. Neuroscience 69(1):83–88

Magarinos AM, McEwen BS (1995b) Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. Neuroscience 69(1):89–98

Magarinos AM, Verdugo JM, McEwen BS (1997) Chronic stress alters synaptic terminal structure in hippocampus. Proc Natl Acad Sci USA 94(25):14002–14008

Maier SF, Amat J, Baratta MV, Paul E, Watkins LR (2006) Behavioral control, the medial prefrontal cortex, and resilience. Dialogues Clin Neurosci 8(4):397–406

Marrosu F, Gessa GL, Giagheddu M, Fratta W (1990) Corticotropin-releasing factor (CRF) increases paradoxical sleep (PS) rebound in PS-deprived rats. Brain Res 515(1–2):315–318

McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87(3):873–904

Meerlo P, Turek FW (2001) Effects of social stimuli on sleep in mice: non-rapid-eye-movement (NREM) sleep is promoted by aggressive interaction but not by sexual interaction. Brain Res 907(1–2):84–92

Meerlo P, Pragt BJ, Daan S (1997) Social stress induces high intensity sleep in rats. Neurosci Lett 225(1):41–44

Meerlo P, de Bruin EA, Strijkstra AM, Daan S (2001a) A social conflict increases EEG slow-wave activity during subsequent sleep. Physiol Behav 73(3):331–335

Meerlo P, Easton A, Bergmann BM, Turek FW (2001b) Restraint increases prolactin and REM sleep in C57BL/6 J mice but not in BALB/cJ mice. Am J Physiol Regul Integr Comp Physiol 281(3):R846–R854

Meerlo P, Mistlberger RE, Jacobs BL, Heller HC, McGinty D (2009) New neurons in the adult brain: the role of sleep and consequences of sleep loss. Sleep Med Rev 13(3):187–194

Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B (2002) REM sleep and the early development of posttraumatic stress disorder. Am J Psychiatry 159(10):1696–1701

Mellman TA, Pigeon WR, Nowell PD, Nolan B (2007) Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. J Trauma Stress 20(5):893–901

Mikkelsen JD, Hay-Schmidt A, Kiss A (2004) Serotonergic stimulation of the rat hypothalamo-pituitary-adrenal axis: interaction between 5-HT1A and 5-HT2A receptors. Ann N Y Acad Sci 1018:65–70

Miklos IH, Kovacs KJ (2003) Functional heterogeneity of the responses of histaminergic neuron subpopulations to various stress challenges. Eur J Neurosci 18(11):3069–3079

Miller RR, Daniel D, Berk AM (1974) Successive reversals of a discriminated preference for signaled tailshock. Anim Learn Behav 2(4):271–274

Mitra R, Jadhav S, McEwen BS, Vyas A, Chattarji S (2005) Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci USA 102(26):9371–9376

Mrdalj J, Pallesen S, Milde AM, Jellestad FK, Murison R, Ursin R, Bjorvatn B, Gronli J (2013) Early and later life stress alter brain activity and sleep in rats. PLoS One 8(7):e69923

Myers KM, Davis M (2007) Mechanisms of fear extinction. Mol Psychiatry 12(2):120–150

Neckelmann D, Mykletun A, Dahl AA (2007) Chronic insomnia as a risk factor for developing anxiety and depression. Sleep 30(7):873–880

Nishida M, Pearsall J, Buckner RL, Walker MP (2009) REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 19(5):1158–1166

Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E (2000) Hypocretin (orexin) deficiency in human narcolepsy. Lancet 355(9197):39–40

Nomura K, Nakao M, Takeuchi T, Yano E (2009) Associations of insomnia with job strain, control, and support among male Japanese workers. Sleep Med 10(6):626–629

Obal F Jr, Kacsoh B, Alfoldi P, Payne L, Markovic O, Grosvenor C, Krueger JM (1992) Antiserum to prolactin decreases rapid eye movement sleep (REM sleep) in the male rat. Physiol Behav 52(6):1063–1068

Obal F Jr, Garcia-Garcia F, Kacsoh B, Taishi P, Bohnet S, Horseman ND, Krueger JM (2005) Rapid eye movement sleep is reduced in prolactin-deficient mice. J Neurosci 25(44):10282–10289

Pacak K, Palkovits M (2001) Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. Endocr Rev 22(4):502–548

Palma BD, Suchecki D, Tufik S (2000) Differential effects of acute cold and footshock on the sleep of rats. Brain Res 861(1):97–104

Pawlyk AC, Morrison AR, Ross RJ, Brennan FX (2008) Stress-induced changes in sleep in rodents: Models and mechanisms. Neurosci Biobehav Rev 32(1):99–117

Paylor R, Tracy R, Wehner J, Rudy J (1994) DBA/2 and C57BL/6 mice differ in contextual fear but not auditory fear conditioning. Behav Neurosci 108:810–817

Petrov T, Krukoff TL, Jhamandas JH (1992) The hypothalamic paraventricular and lateral parabrachial nuclei receive collaterals from raphe nucleus neurons: a combined double retrograde and immunocytochemical study. J Comp Neurol 318(1):18–26

Petrov T, Krukoff TL, Jhamandas JH (1994) Chemically defined collateral projections from the pons to the central nucleus of the amygdala and hypothalamic paraventricular nucleus in the rat. Cell Tissue Res 277(2):289–295

Peyron C, Petit JM, Rampon C, Jouvet M, Luppi PH (1998a) Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. J Neurosci 82(2):443–468

Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, Kilduff TS (1998b) Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18(23):9996–10015

Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106(2):274–285

Pitman RK, Shin LM, Rauch SL (2001) Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. J Clin Psychiatry 62(Suppl 17):47–54

Popa D, El Yacoubi M, Vaugeois JM, Hamon M, Adrien J (2006) Homeostatic regulation of sleep in a genetic model of depression in the mouse: effects of muscarinic and 5-HT1A receptor activation. Neuropsychopharmacology 31(8):1637–1646

Prewitt CM, Herman JP (1997) Hypothalamo-pituitary-adrenocortical regulation following lesions of the central nucleus of the amygdala. Stress 1(4):263–280

Prewitt CM, Herman JP (1998) Anatomical interactions between the central amygdaloid nucleus and the hypothalamic paraventricular nucleus of the rat: a dual tract-tracing analysis. J Chem Neuroanat 15(3):173–185

Price J, Russchen F, Amaral D (1987). The limbic region. II: the amygdaloid complex. In: Swanson L (ed) Handbook of chemical neuroanatomy. Integrated systems of the CNA, Part I. Elsevier, New York, pp 279–375

Rachalski A, Alexandre C, Bernard JF, Saurini F, Lesch KP, Hamon M, Adrien J, Fabre V (2009) Altered sleep homeostasis after restraint stress in 5-HTT knock-out male mice: a role for hypocretins. J Neurosci 29(49):15575–15585

Radley JJ, Morrison JH (2005) Repeated stress and structural plasticity in the brain. Ageing Res Rev 4(2):271–287

Radley JJ, Rocher AB, Miller M, Janssen WG, Liston C, Hof PR, McEwen BS, Morrison JH (2006) Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. Cereb Cortex 16(3):313–320

Rampin C, Cespuglio R, Chastrette N, Jouvet M (1991) Immobilisation stress induces a paradoxical sleep rebound in rat. Neurosci Lett 126(2):113–118

Rojas-Zamorano JA, Esqueda-Leon E, Jimenez-Anguiano A, Cintra-McGlone L, Mendoza Melendez MA, Velazquez Moctezuma J (2009) The H1 histamine receptor blocker, chlorpheniramine, completely prevents the increase in REM sleep induced by immobilization stress in rats. Pharmacol Biochem Behav 91(3):291–294

Roky R, Obâal F Jr, Valatx JL, Bredow S, Fang J, Pagano LP, Krueger JM (1995) Prolactin and rapid eye movement sleep regulation. Sleep 18(7):536–542

Roozendaal B, Koolhaus J, Bohus B (1991a) Attenuated cardiovascular, neuroendocrine, and behavioral responses after a single footshock in central amygdaloid lesioned male rats. Phys Behav 50:771–775

Roozendaal B, Koolhaus J, Bohus B (1991b) Central amygdala lesions affect behavioral and autonomic balance during stress in rats. Phys Behav 50:777–781

Rosenkranz JA, Buffalari DM, Grace AA (2006) Opposing influence of basolateral amygdala and footshock stimulation on neurons of the central amygdala. Biol Psychiatry 59(9):801–811

Rudolph C, Richards GE, Kaplan S, Ganong WF (1979) Effect of intraventricular histamine on hormone secretion in dogs. Neuroendocrinology 29(3):169–177

Sajdyk TJ, Schober DA, Gehlert DR, Shekhar A (1999) Role of corticotropin-releasing factor and urocortin within the basolateral amygdala of rats in anxiety and panic responses. Behav Brain Res 100(1–2):207–215

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richarson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M (1998). Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92(5):1 page following 696

Samson WK, Taylor MM, Follwell M, Ferguson AV (2002) Orexin actions in hypothalamic paraventricular nucleus: physiological consequences and cellular correlates. Regul Pept 104(1–3):97–103

Sandi C, Davies HA, Cordero MI, Rodriguez JJ, Popov VI, Stewart MG (2003) Rapid reversal of stress induced loss of synapses in CA3 of rat hippocampus following water maze training. Eur J Neurosci 17(11):2447–2456

Sanford LD, Tejani-Butt SM, Ross RJ, Morrison AR (1995) Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms. Arch Ital Biol 134(1):81–99

Sanford LD, Nassar P, Ross RJ, Schulkin J, Morrison AR (1998) Prolactin microinjections into the amygdalar central nucleus lead to decreased NREM sleep. Sleep Res Online 1(3):109–113

Sanford LD, Silvestri AJ, Ross RJ, Morrison AR (2001) Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep. Arch Ital Biol 139(3):169–183

Sanford LD, Parris B, Tang X (2002) GABAergic regulation of the central nucleus of the amygdala: implications for sleep control. Brain Res 956(2):276–284

Sanford L, Yang L, Tang X (2003a) Influence of contextual fear on sleep architecture in mice: a strain comparison. Sleep 26:527–540

Sanford LD, Fang J, Tang X (2003b) Sleep after differing amounts of conditioned fear training in BALB/cJ mice. Behav Brain Res 147(1–2):193–202

Sanford LD, Tang X, Ross RJ, Morrison AR (2003c) Influence of shock training and explicit fear-conditioned cues on sleep architecture in mice: strain comparison. Behav Genet 33(1):43–58

Sanford LD, Xiao J, Liu X, Yang L, Tang X (2005) Influence of avoidance training (AT) and AT cues on sleep in C57BL/6 J (B6) and BALB/cJ (C) mice. Sleep (Abstract Supplement) 28:A6

Sanford LD, Yang L, Liu X, Tang X (2006) Effects of tetrodotoxin (TTX) inactivation of the central nucleus of the amygdala (CNA) on dark period sleep and activity. Brain Res 1084(1):80–88

Sanford LD, Yang L, Wellman LL, Liu X, Tang X (2010) Differential effects of controllable and uncontrollable footshock stress on sleep in mice. Sleep 33(5):621–630

Schiffelholz T, Aldenhoff JB (2002) Novel object presentation affects sleep–wake behavior in rats. Neurosci Lett 328(1):41–44

Seltzer AM, Donoso AO, Podesta E (1986) Restraint stress stimulation of prolactin and ACTH secretion: role of brain histamine. Physiol Behav 36(2):251–255

Semba K, Fibiger HC (1992) Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. J Comp Neurol 323(3):387–410

Shors TJ, Seib TB, Levine S, Thompson RF (1989) Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. Science 244(4901):224–226

Silvestri AJ (2005) REM sleep deprivation affects extinction of cued but not contextual fear conditioning. Physiol Behav 84(3):343–349

Sinha RK (2006) P-CPA pretreatment reverses the changes in sleep and behavior following acute immobilization stress rats. Journal Physiol Sci: JPS 56(1):123–129

Smith C (1995) Sleep states and memory processes. Behav Brain Res 69(1–2):137–145

Smith C, Lapp L (1986) Prolonged increases in both PS and number of REMS following a shuttle avoidance task. Physiol Behav 36(6):1053–1057

Smith CT, Miskiman DE (1975) Increases in paradoxical sleep as a result of amygdaloid stimulation. Physiol Behav 15(1):17–19

Smith SM, Vale WW (2006) The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci 8(4):383–395

Steiger A (2007) Neurochemical regulation of sleep. J Psychiatr Res 41(7):537–552

Steiger A, Holsboer F (1997) Neuropeptides and human sleep. Sleep 20(11):1038–1052

Steiger A, Antonijevic IA, Bohlhalter S, Frieboes RM, Friess E, Murck H (1998) Effects of hormones on sleep. Horm Res 49(3–4):125–130

Steiner MA, Sciarretta C, Brisbare-Roch C, Strasser DS, Studer R, Jenck F (2013) Examining the role of endogenous orexins in hypothalamus-pituitary-adrenal axis endocrine function using

transient dual orexin receptor antagonism in the rat. Psychoneuroendocrinology 38(4):560–571
Steriade M, McCarley R (1990) Brainstem control of wakefulness and sleep. Plenum Press, New York
Stewart MG, Davies HA, Sandi C, Kraev IV, Rogachevsky VV, Peddie CJ, Rodriguez JJ, Cordero MI, Donohue HS, Gabbott PL, Popov VI (2005) Stress suppresses and learning induces plasticity in CA3 of rat hippocampus: a three-dimensional ultrastructural study of thorny excrescences and their postsynaptic densities. Neuroscience 131(1):43–54
Suchecki D, Tiba PA, Machado RB (2012) REM sleep rebound as an adaptive response to stressful situations. Frontiers Neurol 3:41
Sutcliffe JG, de Lecea L (2002) The hypocretins: setting the arousal threshold. Nat Rev Neurosci 3(5):339–349
Swerdlow N, Geyer M, Vale W, Koob G (1986) Corticotropin-releasing factor potentiates acoustic startle in rats: blockade by chlordiazepoxide. Psychopharmacology 88:147–152
Takahashi K, Koyama Y, Kayama Y, Yamamoto M (2000) The effects of prolactin on the mesopontine tegmental neurons. Psychiatry Clin Neurosci 54(3):257–258
Tang X, Xiao J, Liu X, Sanford LD (2004) Strain differences in the influence of open field exposure on sleep in mice. Behav Brain Res 154(1):137–147
Tang X, Liu X, Yang L, Sanford LD (2005a) Rat strain differences in sleep after acute mild stressors and short-term sleep loss. Behav Brain Res 160(1):60–71
Tang X, Xiao J, Parris BS, Fang J, Sanford LD (2005b) Differential effects of two types of environmental novelty on activity and sleep in BALB/cJ and C57BL/J mice. Physiol Behav 85:419–429
Tang X, Yang L, Liu X, Sanford LD (2005c) Influence of tetrodotoxin inactivation of the central nucleus of the amygdala on sleep and arousal. Sleep 28(8):923–930
Tang X, Yang L, Sanford LD (2005d) Rat strain differences in freezing and sleep alterations associated with contextual fear. Sleep 28(10):1235–1244
Tang X, Yang L, Sanford LD (2006) Spectral EEG power after uncontrollable shock (US) and fearful context (FC): variability amongst mouse strains. Sleep 29:A11
Tang X, Yang L, Sanford LD (2007) Individual variation in sleep and motor activity in rats. Behav Brain Res 180(1):62–68
Tiba PA, Tufik S, Suchecki D (2004) Effects of maternal separation on baseline sleep and cold stress-induced sleep rebound in adult Wistar rats. Sleep 27(6):1146–1153
Tiba PA, Tufik S, Suchecki D (2008) Long lasting alteration in REM sleep of female rats submitted to long maternal separation. Physiol Behav 93(3):444–452
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10(1):49–62
Tsuda A, Ida Y, Tsujimaru S, Satoh H, Nishimura H, Tanaka M (1987) Stressor controllability and brain noradrenaline turnover in rats. Yakubutsu Seishin Kodo 7(3):363–374
Van Bockstaele EJ, Colago EE, Valentino RJ (1998) Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. J Neuroendocrinol 10(10):743–757
Vertes RP (2004) Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51(1):32–58
Vyas A, Jadhav S, Chattarji S (2006) Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. Neuroscience 143(2):387–393
Walker MP (2009) The role of sleep in cognition and emotion. Ann N Y Acad Sci 1156:168–197
Wellman CL (2001) Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. J Neurobiol 49(3):245–253
Wellman LL, Holbrook BD, Yang L, Tang X, Sanford LD (2008) Contextual fear extinction eliminates sleep disturbances found following fear conditioning in rats. Sleep 31:1035–1042
Wellman LL, Ambrozewicz MA, Yang L, Machida M, Sanford LD (2013) Basolateral amygdala and the regulation of fear conditioned changes in sleep: role of corticotropin releasing factor. Sleep 36:471–480

Winsky-Sommerer R, Yamanaka A, Diano S, Borok E, Roberts AJ, Sakurai T, Kilduff TS, Horvath TL, de Lecea L (2004) Interaction between the corticotropin-releasing factor system and hypocretins (orexins): a novel circuit mediating stress response. J Neurosci 24(50):11439–11448

Winsky-Sommerer R, Boutrel B, de Lecea L (2005) Stress and arousal: the corticotrophin-releasing factor/hypocretin circuitry. Mol Neurobiol 32(3):285–294

Xu L, Anwyl R, Rowan MJ (1997) Behavioural stress facilitates the induction of long-term depression in the hippocampus. Nature 387(6632):497–500

Yang L, Tang X, Wellman LL, Liu X, Sanford LD (2009) Corticotropin releasing factor (CRF) modulates fear-induced alterations in sleep in mice. Brain Res 1276:112–122

Yang L, Wellman LL, Ambrozewicz MA, Sanford LD (2011a) Effects of stressor predictability and controllability on sleep, temperature, and fear behavior in mice. Sleep 34(6):759–771

Yang L, Wellman LL, Tang X, Sanford LD (2011b) Effects of corticotropin releasing factor (CRF) on sleep and body temperature following controllable footshock stress in mice. Physiol Behav 104(5):886–892

Zhu GQ, Zhong MK, Zhang JX, Zhao LZ, Ke DP, Wang M, Shi L (1998) Role of basolateral amygdaloid nuclei in sleep and wakeful state regulation. Sheng Li Xue Bao 50(6):688–692

Ziegler DR, Cass WA, Herman JP (1999) Excitatory influence of the locus coeruleus in hypothalamic-pituitary-adrenocortical axis responses to stress. J Neuroendocrinol 11(5):361–369

Sleep and Emotional Functions

Lampros Perogamvros and Sophie Schwartz

Abstract In this chapter, we review studies investigating the role of sleep in emotional functions. In particular, evidence has recently accumulated to show that brain regions involved in the processing of emotional and reward-related information are activated during sleep. We suggest that such activation of emotional and reward systems during sleep underlies the reprocessing and consolidation of memories with a high affective and motivational relevance for the organism. We also propose that these mechanisms occurring during sleep promote adapted cognitive and emotional responses in the waking state, including overnight performance improvement, creativity, and sexual functions. Activation across emotional-limbic circuits during sleep also appears to promote emotional maturation and the emergence of consciousness in the developing brain.

Keywords Sleep · Sleep deprivation · Dreaming · Emotion · Cognition · Reward · Sexual function · Creativity · Memory consolidation · Brain development · Amygdala · Prefrontal cortex · Hippocampus · Ventral tegmental area · Striatum · Nucleus accumbens · Dopamine · Limbic · Mesolimbic

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Contents

1 Introduction

Recent neuroimaging and neurophysiological findings converge to suggest that emotional and reward networks are activated during sleep (e.g., Braun et al. 1997; Dahan et al. 2007; Lansink et al. 2008; Lena et al. 2005; Maquet et al. 1996; Nofzinger et al. 1997). The main aim of this chapter is to consider how and why such systems are activated during sleep while the organism does not interact with its external environment. The recruitment of emotional and reward circuits during sleep might reflect the affective and motivational components of the dreaming experience. While a link with dreaming is plausible, this proposal may not fully account for the fact that activation of these networks is present across many different species (e.g., rats, humans), and can also be elicited in sleeping babies from 3- to 7-month old of age (Blasi et al. 2011), that is, before the emergence of dream consciousness (Hobson 2009). Here, we review a series of recent studies supporting the hypothesis that the processing of emotional and reward-related information is preserved during sleep, and may offer a major evolutionary advantage for neurophysiological adjustments underlying waking behavioral fitness and emotional well-being.

Sleep complements wakefulness by supporting important cognitive and emotional functions (Desseilles et al. 2011; Stickgold 2005; Walker 2010). Based on experimental data demonstrating that memory replay and consolidation processes occur during all sleep stages (Diekelmann and Born 2010; Maquet 2001; Oudiette et al. 2009; Stickgold 2005), we suggest that the activation of emotional and reward systems during sleep underlies the reprocessing and consolidation of memories with a high affective and motivational relevance for the organism (Perogamvros and Schwartz 2012). We also explain how such activation during sleep contributes to the regulation and preparation of adequate cognitive and emotional responses in

the waking state, including overnight performance improvement, creativity, and sexual functions. In addition, emotional activation during sleep may be a necessary factor for emotional maturation, and the emergence and maintenance of consciousness in the developing brain.

2 Activation of Emotional and Reward Brain Circuits during Sleep

Robust evidence for the activation of emotional and reward networks during sleep comes from neuroimaging and neurophysiological studies.

2.1 Activation of Emotional Networks

During non rapid eye movement (NREM) sleep, decreases in brain activity have consistently been reported, in agreement with a homeostatic need for recovery. More specifically, activity decreases in the brainstem, thalamus, basal ganglia, basal forebrain and in several cortical areas including the medial prefrontal cortex (PFC) and precuneus (Dang-Vu et al. 2010). However, recent functional MRI studies have revealed event-related increases in activity during NREM sleep. In particular, NREM sleep spindles (i.e., bursts of oscillatory brain activity with a frequency of 12–14 Hz that are visible in the EEG) appear to be associated with increased activity in the lateral and posterior thalamus, as well as in emotion-related regions such as the anterior cingulate cortex (ACC), insula, and superior temporal gyrus (Schabus et al. 2007). Slow waves (i.e., slow oscillatory brain activity with a frequency <1 Hz, which is the most prominent EEG feature of NREM sleep) have been associated with increased activity in the parahippocampal gyrus, precuneus, and posterior cingulate cortex (Dang-Vu et al. 2008). In addition, bilateral increases in regional metabolism from waking to NREM have been found in the ventral striatum, anterior cingulate cortex, and extensive regions of the medial temporal lobe, including the amygdala and hippocampus (Nofzinger et al. 2002).

Rapid eye movement (REM) sleep is characterized by the activation of several emotion-related brain regions, including the bilateral amygdala, the medial temporal lobe with the hippocampal formation, the medial PFC, and the ACC (Braun et al. 1997; Maquet et al. 1996; Nofzinger et al. 1997) (Fig. 1). On the one hand, the amygdala, along with the brainstem, is involved in the cardiovascular regulation during sleep (Desseilles et al. 2006), and may thus reflect autonomic regulation in response to intense emotions, in particular fear and anxiety that are often experienced in dreams (Schwartz and Maquet 2002; Smith et al. 2004). On the other hand, amygdala connections with the hippocampus, thalamus, medial PFC,

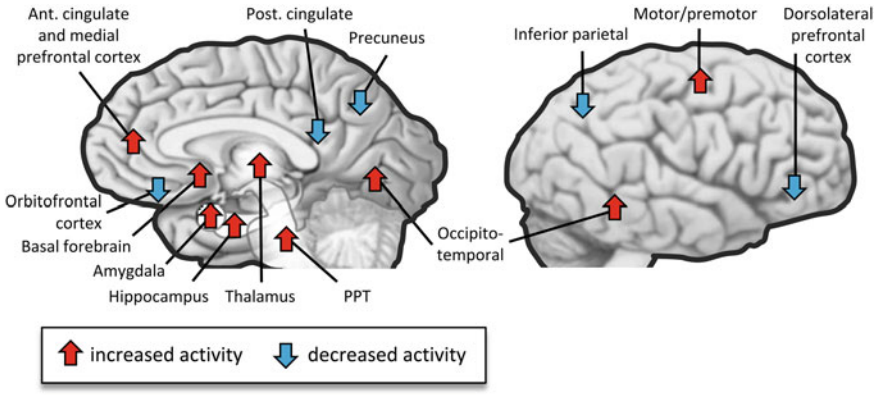

Fig. 1 Functional neuroanatomy of human REM sleep. Brain regions more activated during REM sleep are indicated with an upward red arrow, and those less activated are indicated with a downward blue arrow. Data from studies using PET imaging (Braun et al. 1997, 1998; Maquet et al. 1996, 2000; Nofzinger et al. 1997). *PPT* penduculopontine tegmental nuclei. Adapted from Perogamvros and Schwartz (2012)

and ACC have an important role in assigning affective values to stimuli and thus potentially strengthening stimulus-outcome associations (see Sect. 3.5 below).

Contrasting with the activation of emotion-related regions, several structures implicated in executive and attentional functions during wakefulness are significantly deactivated during REM sleep, including the dorsolateral PFC, precuneus, orbitofrontal cortex, and the inferior parietal cortex (Braun et al. 1997; Maquet et al. 1996, 2000, 2005; Nofzinger et al. 1997). Deactivations in these regions may be responsible for several typical features in the dream experience such as disorientation, illogical thinking, reduced attention and cognitive control, and impaired working memory in dreaming (Hobson et al. 1998; Schwartz 2004; Schwartz and Maquet 2002). Regional cerebral activations and deactivations during REM sleep are shown in Fig. 1.

Taken together these studies suggest substantial activation of emotional networks during all stages of sleep that may be more persistent and less variable during REM sleep than during NREM sleep.

2.2 Activation of Reward Networks

The reward system contributes to the development and monitoring of goal-directed and adaptive behaviors in all mammals, including humans. The reward system is responsible for the processing of rewards or punishers, which typically serve respectively as positive or negative signals for behavioral adaptation and learning. In this way, reward processing is often associated with the feeling of anticipation while

seeking a reward and the pleasure when obtaining it. On the other hand, punishers can induce emotional states such as anger or fear and elicit withdrawal behavior. In addition to brain regions involved in emotional regulation, brain areas that are more specifically involved in the regulation of reward are also activated during sleep, including the ventral tegmental area (VTA) and the nucleus accumbens (NAcc) (see Fig. 3). These activations during sleep likely contribute to the reprocessing of memories with a high emotional or motivational relevance, in coordination with emotion-related circuits (for a review, see Perogamvros and Schwartz 2012).

Two studies have demonstrated that dopaminergic neurons in the VTA of rats increase their bursting activity during REM sleep, which results in a large synaptic dopamine release in the NAcc shell (Dahan et al. 2007; Maloney et al. 2002). This activity is significantly higher during REM sleep as compared to NREM sleep and relaxed or quiet wakefulness. In fact, VTA activation during REM sleep is comparable in intensity and duration to VTA activation during feeding or sex. A second important region for reward processing is the NAcc, whose activity is typically greatest for large rewards (Cooper and Knutson 2008). Activity in the NAcc is increased during REM sleep (Lena et al. 2005). Other reward-related regions, like the ventromedial PFC (Haber and Knutson 2010) and the ACC, which assign a positive or negative value to future outcomes (Bush et al. 2002; Takenouchi et al. 1999), are activated during REM sleep, in both animals and humans (Lena et al. 2005; Maquet et al. 1996, 2000). In addition, neuronal activity in the hippocampus displays a theta rhythm (i.e., an oscillatory pattern in EEG with a frequency range of 5-12 Hz in behaving rats and 4-7 Hz in humans) during REM sleep in both animals (Popa et al. 2010; Winson 1972) and humans (Cantero et al. 2003) studies. This latter finding is remarkable considering that increased theta oscillations have been reported during novelty-seeking, exploratory and instinctual behaviors, which are also seen in REM sleep behavior disorder and other parasomnias (Perogamvros et al. 2012). Finally, the orexin/hypocretin neurons in the lateral hypothalamus have transient discharges during REM sleep (Mileykovskiy et al. 2005; Takahashi et al. 2008). The orexin/hypocretin system is particularly interesting because it plays a key role in both the regulation of sleep–wake states and emotional/motivated behaviors, via strong functional interactions with the mesolimbic dopamine circuitry (Harris et al. 2005; Ponz et al. 2010a, b; Schwartz et al. 2008; Thompson and Borgland 2011).

Activation of reward-related regions is, in some cases, also observed during NREM sleep. In particular, a spontaneous reactivation (or replay) of neuronal firing patterns occurs in the ventral striatum of rats after a reward searching behavior (Lansink et al. 2008; Pennartz et al. 2004). This off-line replay is induced by hippocampal ripples and seems to be related to linking a memory trace to a motivational or emotional value during sleep (Lansink et al. 2009). Whether a similar neural mechanism exists in humans is still unclear, but brain imaging studies have demonstrated that the hippocampus and the ventral striatum are also activated during NREM sleep (Nofzinger et al. 2002), and that increased hippocampal activity may relate to subsequent performance improvement

(Peigneux et al. 2004). Some other reward-related regions are also found to be activated during NREM sleep, like the posterior insula, ACC (Schabus et al. 2007), and the amygdala (Nofzinger et al. 2002).

3 Implications of Emotional/Motivational Networks Activation during Sleep

3.1 Emotional Maturation

> The function of the brain which is most influenced by sleep is the memory; not that it entirely ceases; but it is brought back to a condition of imperfection, such as everyone may have experienced in pre-historic times, whether asleep or awake (Friedrich Nietzsche, 1878, "Human, All Too Human", section one: "Of First and Last Things", aphorism #12).

According to Nietzsche, the mind in sleep regresses to an archaic state of waking reasoning and consciousness, resembling that of early mankind. More than one century later, Jaak Panksepp claimed that an archaic affective state is expressed in REM sleep and dreams (Panksepp 1998), while Allan Hobson suggested that REM sleep is a protoconsciousness state preceding the maturity of the waking consciousness (Hobson 2009, see also Koukkou and Lehmann 1993).

Recent studies support the role of sleep in emotional maturity of the human. Since as early as the 13th week of gestation and neonatal period, smiles and other expressions are extremely common, especially during active REM sleep (Dondi et al. 2007; Emde and Koenig 1969; Messinger et al. 2002). The recent work of Messinger and collaborators showed that neonatal smiles, in particular Duchenne smiles that involve cheek raising and index positive emotion (Ekman 1992), are more frequent, stable, and enduring during active sleep (corresponding to adult REM sleep, Roffwarg et al. 1966) than during other behavioral states (Dondi et al. 2007; Messinger and Fogel 2007) (Fig. 2). These authors put forward the interesting hypothesis that such smiles could relate to the activation of the amygdala and limbic structures during REM sleep (see Sect. 2 above), and may foster the functional coordination of facial motor programs with neural structures supporting the emotional and social expression of smiling later in development (at about 2 months of age) (Dondi et al. 2007).

Recent imaging data in 3- to 7-month olds infants also revealed specific brain responses to emotional human vocalizations during sleep, involving the orbitofrontal cortex and insula (Blasi et al. 2011). Furthermore, it is noteworthy that active (or REM) sleep occupies the biggest portion of a child's sleep and occurs much earlier in human development than proper dreaming (Foulkes 1993). Altogether, these data suggest that REM sleep of infants is likely to subserve crucial emotional (Berger et al. 2012; Perogamvros 2012) and learning functions (Fifer et al. 2010), much like what is found in adults (Sterpenich et al. 2009; Wagner et al. 2001) (see Sect. 3.5). However, these data should not eclipse the possible

Fig. 2 Smile of a 42-hour-old sleeping infant. Typical Duchenne smile with cheek raising which is thought to relate to the experience of positive emotion (*see main text*). Reproduced from Messinger et al. (2002) with permission

contribution of sleep structure and NREM sleep (quiet sleep in newborns) to these important functions. Indeed, a recent study tested whether sleep–wake transitions in the neonatal period might predict emotional and cognitive development in premature infants during the first 5 years of life (Weisman et al. 2011). Sleep states at a gestational age of 37 weeks, emotional regulation during infant–mother and infant–father interactions at 3 and 6 months, cognitive development at 6, 12, and 24 months, as well as verbal IQ, executive functions, and symbolic competence at 5 years were assessed. It was shown that sleep-state transitions characterized by shifts between quiet sleep and wakefulness (contrary to rapid cycles between states of high arousal, such as active sleep and cry) are important for an optimal emotional and cognitive development, at least in premature infants.

3.2 Dreaming

Recent empirical research on dreaming favors a relatively broad definition of dreaming as corresponding to any internally generated sensory, motor, emotional or cognitive subjective experiences that occur during sleep. Our neurobiological knowledge about human dreaming derives primarily from the study of REM sleep, because this sleep stage has initially been linked to dreaming activity (Dement and Kleitman 1957). However, dreaming may occur in any sleep stage (i.e., both REM and NREM sleep stages) (Foulkes 1996; Oudiette et al. 2012), although distinct phenomenological characteristics differentiate REM from NREM dreaming. For example, dream reports are on average more vivid, bizarre, with complex narratives, i.e., more 'dream-like', after awakenings from REM sleep than from NREM sleep (Fosse et al. 2001; Strauch and Meier 1996). In addition, REM dreaming is characterized by content with emotional and motivational value (e.g., socializing, fighting, or sexual activity). Note that daily routine activities such as typing, washing dishes, or buying food at the supermarket are generally not frequent in dream reports (Schredl 2010). Motivational and emotional content is more prominent in REM than in NREM dreaming (Smith et al. 2004). This is consistent with the finding that several limbic and mesolimbic dopaminergic regions are

selectively activated during REM sleep, amygdala activity and burst firing in the VTA being significantly higher in REM sleep compared to NREM sleep. Moreover, lesion studies abolishing REM sleep muscle atonia in cats, revealed a predominance of seeking (e.g., spatial exploration) and emotional behaviors (e.g., anger) during enacted behaviors in REM (or paradoxical) sleep (Jouvet 1965). Similarly, aggressive behaviors, but also seeking types of behaviors (such as mimicking eating, drinking, smoking a cigarette, etc.), are also frequent in patients with REM sleep behavior disorder, who act out their dreams (Oudiette et al. 2009).

To account for the high prevalence of fear-related experiences in dreams, the psychologist and philosopher Revonsuo (2000) proposed the Threat Simulation Theory, according to which dreaming allows an organized and selective offline simulation of threatening events that promotes the development and maintenance of threat-avoidance skills during wakefulness. Realistic threatening experiences in a dream would thus activate threat-related brain circuits, in particular the amygdala, and would lead to improved performance in real life situations (Valli and Revonsuo 2009). Interestingly, individuals suffering from post-traumatic stress disorder simulate threatening events in their dreams more often than controls (Valli et al. 2005), and REM sleep deprivation impairs threat avoidance skills in waking life (Martinez-Gonzalez et al. 2004). Actually, it has been proposed that experiencing threatening stimuli (objects, situations, thoughts, memories, and physical sensations) in a totally safe context during dreaming may resemble exposure therapy for anxiety disorders (Desseilles et al. 2011; Pace-Schott et al. 2009). Nightmares such as in post-traumatic stress disorder would by contrast reflect the failure of an adaptive fear memory extinction process, in the presence of temporary (e.g., daily concerns) or more persistent (e.g., trauma) increases in affect load (Nielsen and Levin 2007). Yet, whether the off-line reprocessing of emotional information requires conscious experience such as in dreaming remains unresolved.

We previously proposed the Reward Activation Model for sleep and dreaming (Perogamvros and Schwartz 2012), according to which emotional memories are prioritized for offline reprocessing (see Sect. 3.5) through the activation during sleep (and not necessarily in dreams) of the SEEKING system. The latter corresponds to an emotional and motivational system of the mammalian brain, which is related to approach behaviors and to the intense feeling of anticipation while seeking a reward (Panksepp 1998). More specifically, sleep would favor the activation of stimulus representations or behaviors of high emotional and motivational relevance, which induce instinctual behaviors or drives (such as feeding, mating, fighting, fleeing, etc.), as well as approach and avoidance behaviors. In our model, emotionally relevant experiences (including threat-related information) have a higher probability of being activated during sleep and have a preferential access to sleep-related memory consolidation processes. It is thus proposed here that one of the main functions of dreaming is to expose the sleeper to rewarding or aversive stimuli, in order to maintain and improve offline memory consolidation processes and performance in real life situations, while also contributing to emotion regulation processes. The reader may refer to Perogamvros and Schwartz (2012) for a detailed description of the Reward Activation Model.

3.3 Sexuality in Sleep

Surprisingly, although sexual content is prominent in dreams (Freud 1900; Schredl 2010), to our knowledge no neurophysiological interpretation of sexual dreaming has yet been proposed. The sexual content of dreams can be regarded as an expression of the activation of reward-related functions during sleep and thus be viewed under the scope of the Reward Activation Model (Perogamvros and Schwartz 2012). Mesolimbic activation during sleep would indeed create a favorable neurophysiological environment for the elicitation of approach behaviors, including those triggered by primary rewards such as sex. Recent neuroimaging studies on sexual stimulation and orgasm in humans confirmed activations across reward and emotional networks (VTA, striatum, insula), but also revealed simultaneous deactivations in structures related to monitoring and cognitive control (prefrontal and orbitofrontal cortex) (Georgiadis et al. 2007; Holstege and Georgiadis 2004; Holstege and Huynh 2011). Notably, these activation/deactivation patterns are also typically observed during REM sleep (see Sect. 2 above). Therefore, activation of reward-related structures (VTA, insula) may favor the elicitation of primary rewards, including sex, in the dreams, whereas deactivation of attentional and cognitive control structures (e.g., parietal cortex, dorsolateral PFC; Sect. 2.1) and the partial disconnection from external sensory inputs, may support relaxation of sexual behavior from social or moral constraints.

Interestingly, testosterone levels in humans increase during the first part of the night, peaking during the first REM periods, and are then stable until awakening (Luboshitzky et al. 1999). This hormonal modulation depends on sleep and not on circadian factors since testosterone levels in young men rise during daytime sleep just as in nighttime sleep, while the levels fall upon waking (Axelsson et al. 2005). The picture is much less clear for women because of the complexity of measuring hormonal levels across the menstrual cycle and many other confounding factors, such as the use of birth control pills. The data available so far point to a direct effect of sleep on the activity of the neuroendocrine reproductive control, ultimately improving sexual satisfaction (Andersen et al. 2011).

Taken together these findings suggest that increased dopaminergic and hormonal activity, and decreased PFC monitoring may contribute to both promoting sexually relevant content in dreams and eliciting sexual arousal during REM sleep. Yet, future correlation studies among dream content, sexual arousal, and hormonal activation are needed to clarify whether the occurrence of spontaneous sexual arousal during REM sleep (Bancroft 2005; Fisher et al. 1983; Karacan et al. 1975) and sexual dreams are independent expressions of a common underlying neurophysiological mechanism (Lamid 1986), whether sexual content of dreams may trigger physiological sexual arousal, or whether the latter may infiltrate the content of the dreams.

3.4 Insight and Creativity

The role of sleep in problem solving and creativity is more than a folk belief. Indeed, in addition to its deleterious impact on reward and emotional functions (Sect. 4), sleep deprivation (SD) impairs affectively guided decision making (Pace-Schott et al. 2012), moral reasoning (Killgore et al. 2007), insight (Wagner et al. 2004), and creativity (Cai et al. 2009; Home 1988). Based on the 'carry-over effect' after awakening (during which performance is altered as a result of the brain's slow transition to full wakefulness), elegant studies by Stickgold and colleagues showed that subjects awoken from REM sleep had a 32 % advantage in the number of anagrams solved (Walker et al. 2002) and also showed greater priming by weak primes (e. g., thief-wrong) than by strong primes (e.g., hot–cold), contrary to the pattern of priming observed during wakefulness (Stickgold et al. 1999). These data are consistent with a hyperassociative state of the mind during REM sleep.

Brain activity during sleep may partly explain these findings. Mesolimbic dopamine activation during sleep may influence novelty seeking and creative drive (Perogamvros and Schwartz 2012). Indeed, the dopaminergic system is thought to contribute to creativity, in particular divergent thinking, cognitive flexibility, innovative insights, and associative thinking (Chermahini and Hommel 2010; Flaherty 2005; Takeuchi et al. 2010). Further evidence comes from Parkinson's disease patients under dopaminergic treatment, who may show increased artistic drive and productivity (Inzelberg 2013; Kulisevsky et al. 2009). Besides increased dopaminergic activity, thalamic gating of external information and deactivation of monitoring regions such as the dorsolateral PFC during (REM) sleep (Maquet et al. 1996), a structure that typically mediates volitional control of ongoing performance, may also provide additional favorable conditions for creativity, by suspending monitoring constraints on mental processes (de Manzano et al. 2010; Limb and Braun 2008). Whether increased creative drive during sleep constitutes a mechanism by which dreams may enhance creativity or facilitate the resolution of emotional conflicts remains to be addressed in future studies (Desseilles et al. 2011; Schredl 2010).

3.5 Off-Line Processing and Consolidation of Emotional Memories

Memory consolidation is an open-ended process by which new memories are progressively reorganized and incorporated into pre-existing long-term memory networks (Wang and Morris 2010). Several studies have shown that memory replay and consolidation processes occur during all sleep stages (for reviews, see Diekelmann and Born 2010; Maquet 2001; Oudiette and Paller 2013; Stickgold 2005). Both slow oscillations and sleep spindles during NREM sleep have been

reported to be associated with memory (procedural and declarative) consolidation and synaptic plasticity processes (Bergmann et al. 2008; Diekelmann and Born 2010; Fogel and Smith 2011; Huber et al. 2004; Marshall et al. 2006; Rosanova and Ulrich 2005). In addition, neuroimaging studies in humans have demonstrated that NREM and REM sleep may foster lasting neural changes as well as changes in functional connectivity after perceptual, motor, or emotional learning tasks (Maquet et al. 2003; Payne and Kensinger 2010; Schwartz et al. 2002; Sterpenich et al. 2007). It is supposed that the neural traces coding for newly acquired information are reactivated during subsequent periods of both NREM sleep and/or REM sleep, thus promoting memory consolidation and reorganization (Diekelmann and Born 2010; Maquet et al. 2000; Oudiette and Paller 2013; Rasch et al. 2007; Rudoy et al. 2009). Below we report converging evidence suggesting that the activation of limbic, paralimbic, and reward systems during sleep—with or without concomitant dream experience—serves emotional regulation and memory consolidation processes.

During NREM sleep, activation of the hippocampus and ventral striatum enables the formation of a memory trace comprising contextual, emotional, and motivational components (Lansink et al. 2009). The coordinated reactivation of both the hippocampus and the ventral striatum during SWS provides a possible mechanism for the consolidation of associative memory-reward information (Fig. 3). In particular, the activation of neurons in the ventral striatum during SWS would support the selection of memories with a high storage priority (Lansink et al. 2008) and may lead to the optimization of adapted behavior during wakefulness. Consistent with this hypothesis, recent data in humans suggest that overnight consolidation of declarative memory and skill learning is guided by emotional relevance and motivational biases (Fischer and Born 2009; Sterpenich et al. 2009; Wilhelm et al. 2011).

Active memory processing may also be consistent with sustained reward-related bursting activity of the VTA (Dahan et al. 2007) and NAcc (Lena et al. 2005) observed in rodents during REM sleep. Phasic VTA dopamine signals during REM sleep could indeed favor an off-line replay of recent emotional memory traces during this sleep stage (Walker and van der Helm 2009). These memories would then serve both as salient and novel stimuli for the penduculopontine tegmental nuclei and VTA, because recent relevant memories (e.g., emotional events, current concerns) are activated in the absence of cognitive control from dorsolateral PFC during REM sleep (Fosse et al. 2003; Schwartz 2003) (Fig. 3). This particular component of our original model still requires support from future studies (Perogamvros and Schwartz 2012).

During REM sleep, robust activation of limbic circuits is thought to promote neuronal reorganization of emotional memory traces. This reorganization involves an enhancement of the functional connectivity between the amygdala, the medial PFC, and the occipital cortex, as well as a progressive transfer of some memories along a hippocampal-cortical route (Frankland and Bontempi 2005; Sterpenich et al. 2009). Further supporting the role of REM sleep in neuronal potentiation processes, REM SD impairs the induction of hippocampal long-term potentiation in

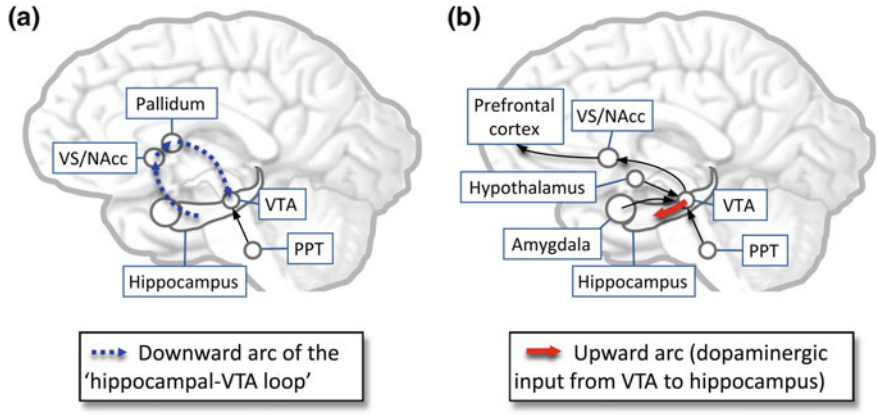

Fig. 3 Schematic illustration the reciprocal interactions between emotion/reward-related regions and hippocampal/prefrontal memory processes during NREM and REM sleep. **a** During NREM sleep, hippocampal activation triggers a spontaneous reactivation (replay) in ventral striatum neurons, which involves the transfer of novelty/relevance signals from the hippocampus to the VTA (*thick dashed blue arrow*). VTA is activated during the transition from a NREM episode to REM sleep, with induction of both tonic (hippocampus–VTA projection) and phasic (PPT–VTA) increase of dopamine. **b** During all REM sleep, increased bursting activity (phasic response) in the VTA may represent stimulus saliency and could fulfill reward-related functions, like stimulus-reward associations and novelty-seeking. During REM sleep, several VTA projections are activated, including the upward arc of hippocampal–VTA loop (dopaminergic input from the VTA to the hippocampus; *thick plain red arrow*), the NAcc, the amygdala, the orexin/hypocretin neurons, the ACC, and the PFC. All these regions have strong anatomical and functional links with the hippocampus and VTA (among others). Activation of the upward arc of the hippocampal–VTA loop contributes to synaptic plasticity and learning by enhancing long-term potentiation (Lisman and Grace 2005). *PPT* penduculopontine tegmental nuclei, *VS/NAcc* ventral striatum/nucleus accumbens, *VTA* ventral tegmental area. Adapted from Perogamvros and Schwartz (2012)

the visual cortex (Shaffery et al. 2002) and in the dorsal hippocampus (Ravassard et al. 2009) of rats. In addition, REM SD impairs hippocampal neurogenesis, which is thought to play a role in memory formation (Meerlo et al. 2009).

Taken together, these results confirm that all stages of sleep contribute to the consolidation of relevant memories involving lasting reorganization within cerebral networks.

4 Sleep Disturbance Causes Waking Emotional Dysfunctions

Early studies have shown that sleep disturbances can affect stress coping and lead to emotional and cognitive dysfunctions. In rats, suppression of REM sleep during the second and third weeks of postnatal development was found to cause anxiety,

decrease in sexual activity (see also Sect. 3.3 above), and structural reductions in the cerebral cortex and brainstem weight in adulthood (Mirmiran et al. 1983). In humans, adaptation to stress was found deficient after REM SD or total SD (Kahn-Greene et al. 2007). In addition, chronic sleep disruption is associated with cognitive performance deficits (Fortier-Brochu et al. 2012; Van Dongen et al. 2003), increased aggressiveness (Kamphuis et al. 2012), and negative mood states (Zohar et al. 2005).

What may be the neurophysiological mechanisms underlying these adverse effects of sleep disturbance? In the light of recent findings on the consequences of total SD and REM SD on decision making and reward function (Gujar et al. 2011; Hanlon et al. 2010; Venkatraman et al. 2007; Yoo et al. 2007), we suggest that sleep contributes to maintaining the integrity of emotional and reward brain networks (Sects. 2.1 and 2.2). Indeed, total or partial SD impairs the normal functioning of these networks. For example, after SD, activation of the NAcc was exacerbated for risky choices in a game-like task, while insular and orbitofrontal responses to losses were reduced, denoting a diminished reactivity to punishment (Venkatraman et al. 2007). These results convincingly demonstrate that SD may disrupt competent decision making by modulating brain regions associated with risky decision making and emotional processing, such as the NAcc and the insula. Because the insular cortex is activated during both NREM (Nofzinger et al. 2002) and REM sleep (Maquet et al. 2000), one could hypothesize that SD interferes with emotional functions subserved by the insula. Moreover, decreases in D2/D3 receptor availability may account for impairments in performance, reward learning, and decision making after SD (Volkow et al. 2012). Indeed, insufficient sleep is associated with changes in reward-related decision making: people take greater risks (Harrison and Horne 2000) and are less concerned with the negative consequences of their risky behaviors (Chee and Chuah 2008; Venkatraman et al. 2007, 2011).

SD was also found to cause a failure of top-down control from the medial PFC on the amygdala. In one recent fMRI study, two groups of healthy subjects were shown 100 images ranging from emotionally neutral to increasingly aversive during a functional MRI session after one night of sleep deprivation (SD group, $n = 14$) or after one night of sleep (control group, $n = 12$) (Yoo et al. 2007). While both groups expressed similar amygdala activation levels for the neutral pictures, the sleep-deprived subjects exhibited increased amygdala response to the most negative picture stimuli compared to the control group. Importantly, a loss of functional connectivity between the medial PFC and the amygdala in the SD group was also observed. These results suggest that SD causes a reduction of prefrontal control over the limbic system, resulting in an accentuation of emotional responses to negative stimuli. SD may also lead to an amplified reactivity of reward networks in response to positive emotional stimuli (Gujar et al. 2011). More specifically, compared to a non sleep-deprived control group, sleep-deprived participants judged pleasure-evoking stimuli as more pleasant, and showed increased activation in the VTA, left putamen, amygdala and left insula. These regional increases were associated with a reduction in functional connectivity in medial and orbitofrontal

cortex. Together, these studies suggest that sleep loss may impose a bidirectional affective imbalance, including increased behavioral and neural reactivity to both positive and negative emotional stimuli.

While emotional functions are influenced by processes occurring during sleep, as reviewed in the section above, the sleep/wake cycle also influences mood via two other components: the circadian (circadian phase) and homeostatic processes (duration of prior wakefulness) (Boivin et al. 1997). Even a minimal misalignment between circadian phase and sleep phase can deteriorate mood (Danilenko et al. 2003), which may also in part explain mood-related problems (e.g., irritability) in jet-lag (Waterhouse et al. 2005), and severity of unipolar depression (Hasler et al. 2010). Stress can also disrupt the circadian cycle (Meerlo et al. 2002), leading to depressive episodes in vulnerable individuals (Ehlers et al. 1988). In addition, mood deteriorates with increases in the duration of prior wakefulness (Birchler-Pedross et al. 2009; Boivin et al. 1997). The nature of the circadian-homeostatic interaction is such that moderate changes in the timing of the sleep–wake cycle may have profound effects on subsequent mood. In addition, light, with its effects on circadian and non-circadian systems, seems to play a primordial role in mood regulation (Stephenson et al. 2012).

Collectively, these data suggest that sleep disturbance may impact reward brain systems in ways that exacerbate behavioral problems (e.g., increased risk-taking, reduced sensitivity to punishment) and induce emotional lability. Dysregulation of the emotional and reward networks normally activated during sleep (see Sect. 2) also likely explains why sleep disturbance may precede clinical depression by facilitating the occurrence of the depressive reward-deficient symptomatology (anhedonia, aboulia, impaired decision making) (Der-Avakian and Markou 2012; Perogamvros and Schwartz 2012). Actually, insomnia represents an independent major risk factor for the development of major depression (Buysse et al. 2008; Johnson et al. 2006; Riemann and Voderholzer 2003; Roane and Taylor 2008). Thus, sleep deprivation may have major health implications in adolescents and adults, by altering reward and emotional processing.

5 Conclusions

In this chapter, we review evidence supporting that sleep is of critical importance for emotional and reward functions. In particular, activation of emotional-limbic and reward networks during NREM and REM sleep causes a selective replay and consolidation of memories by prioritizing the processing of emotionally and motivationally relevant information. This activation also contributes to emotional maturation, enhanced creativity and insight, overnight performance improvement, the generation of dreams, and may influence sexual functions. We also show that recent findings converge to suggest that optimal mood regulation depends on balanced activity and connectivity within limbic and prefrontal circuits (e.g., amygdala-medial PFC). Thus, sleep disturbance (e.g., insomnia, sleep deprivation)

may result in emotional distress and reward-related dysfunction, which in turn may precipitate mood disorders. The integration of existing data from various research fields, as proposed in this chapter, provides a better understanding of the multi-faceted role of sleep in emotional functions and demonstrates that sleep is a key component of mental health and well-being. It also identifies major challenges and questions that will keep clinicians and researchers busy for the next decade or so, among which the reverberation of neural activity during sleep emerges as a central mechanism promoting waking behavioral fitness as well as the recalibration of the emotional mind.

References

Andersen ML, Alvarenga TF, Mazaro-Costa R, Hachul HC, Tufik S (2011) The association of testosterone, sleep, and sexual function in men and women. Brain Res 1416:80–104

Axelsson J, Ingre M, Akerstedt T, Holmback U (2005) Effects of acutely displaced sleep on testosterone. J Clin Endocrinol Metab 90:4530–4535

Bancroft J (2005) The endocrinology of sexual arousal. J Endocrinol 186:411–427

Berger RH, Miller AL, Seifer R, Cares SR, Lebourgeois MK (2012) Acute sleep restriction effects on emotion responses in 30- to 36-month-old children. J Sleep Res 21:235–246

Bergmann TO, Molle M, Marshall L, Kaya-Yildiz L, Born J, Roman Siebner H (2008) A local signature of LTP- and LTD-like plasticity in human NREM sleep. Eur J Neurosci 27:2241–2249

Birchler-Pedross A, Schroder CM, Munch M, Knoblauch V, Blatter K, Schnitzler-Sack C, Wirz-Justice A, Cajochen C (2009) Subjective well-being is modulated by circadian phase, sleep pressure, age, and gender. J Biol Rhythms 24:232–242

Blasi A, Mercure E, Lloyd-Fox S, Thomson A, Brammer M, Sauter D, Deeley Q, Barker GJ, Renvall V, Deoni S, Gasston D, Williams SC, Johnson MH, Simmons A, Murphy DG (2011) Early specialization for voice and emotion processing in the infant brain. Curr Biol 21:1220–1224

Boivin DB, Czeisler CA, Dijk DJ, Duffy JF, Folkard S, Minors DS, Totterdell P, Waterhouse JM (1997) Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. Arch Gen Psychiatry 54:145–152

Braun AR, Balkin TJ, Wesensten NJ, Gwadry F, Carson RE, Varga M, Baldwin P, Belenky G, Herscovitch P (1998) Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 279:91–95

Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, Selbie S, Belenky G, Herscovitch P (1997) Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain 120(Pt 7):1173–1197

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002) Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc Natl Acad Sci U S A 99:523–528

Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rossler W (2008) Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep 31:473–480

Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC (2009) REM, not incubation, improves creativity by priming associative networks. Proc Natl Acad Sci U S A 106:10130–10134

Cantero JL, Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B (2003) Sleep-dependent theta oscillations in the human hippocampus and neocortex. J Neurosci 23:10897–10903

Chee MW, Chuah LY (2008) Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. Curr Opin Neurol 21:417–423

Chellappa SL, Schroder C, Cajochen C (2009) Chronobiology, excessive daytime sleepiness and depression: is there a link? Sleep Med 10:505–514

Chermahini SA, Hommel B (2010) The (b)link between creativity and dopamine: spontaneous eye blink rates predict and dissociate divergent and convergent thinking. Cognition 115:458–465

Cooper JC, Knutson B (2008) Valence and salience contribute to nucleus accumbens activation. Neuroimage 39:538–547

Dahan L, Astier B, Vautrelle N, Urbain N, Kocsis B, Chouvet G (2007) Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep. Neuropsychopharmacology 32:1232–1241

Dang-Vu TT, Schabus M, Desseilles M, Albouy G, Boly M, Darsaud A, Gais S, Rauchs G, Sterpenich V, Vandewalle G, Carrier J, Moonen G, Balteau E, Degueldre C, Luxen A, Phillips C, Maquet P (2008) Spontaneous neural activity during human slow wave sleep. Proc Natl Acad Sci U S A 105:15160–15165

Dang-Vu TT, Schabus M, Desseilles M, Sterpenich V, Bonjean M, Maquet P (2010) Functional neuroimaging insights into the physiology of human sleep. Sleep 33:1589–1603

Danilenko KV, Cajochen C, Wirz-Justice A (2003) Is sleep per se a zeitgeber in humans? J Biol Rhythms 18:170–178

de Manzano O, Cervenka S, Karabanov A, Farde L, Ullen F (2010) Thinking outside a less intact box: thalamic dopamine D2 receptor densities are negatively related to psychometric creativity in healthy individuals. PLoS ONE 5:e10670

Dement W, Kleitman N (1957) Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol 9:673–690

Der-Avakian A, Markou A (2012) The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci 35:68–77

Desseilles M, Dang-Vu TT, Sterpenich V, Schwartz S (2011) Cognitive and emotional processes during dreaming: a neuroimaging view. Conscious Cogn 20:998–1008

Desseilles M, Vu TD, Laureys S, Peigneux P, Degueldre C, Phillips C, Maquet P (2006) A prominent role for amygdaloid complexes in the variability in heart rate (VHR) during rapid eye movement (REM) sleep relative to wakefulness. Neuroimage 32:1008–1015

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126

Dondi M, Messinger D, Colle M, Tabasso A, Simion F, Dalla Barba B, Fogel A (2007) A new perspective on neonatal smiling: differences between the judgments of expert coders and naive observers. Infancy 12:235–255

Ehlers CL, Frank E, Kupfer DJ (1988) Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. Arch Gen Psychiatry 45:948–952

Ekman P (1992) An argument for basic emotions. Cogn Emot 6:169–200

Emde RN, Koenig KL (1969) Neonatal smiling, frowning, and rapid eye movement states. II. Sleep-cycle study. J Am Acad Child Psychiatry 8:637–656

Fifer WP, Byrd DL, Kaku M, Eigsti IM, Isler JR, Grose-Fifer J, Tarullo AR, Balsam PD (2010) Newborn infants learn during sleep. Proc Natl Acad Sci U S A 107:10320–10323

Fischer S, Born J (2009) Anticipated reward enhances offline learning during sleep. J Exp Psychol Learn Mem Cogn 35:1586–1593

Fisher C, Cohen HD, Schiavi RC, Davis D, Furman B, Ward K, Edwards A, Cunningham J (1983) Patterns of female sexual arousal during sleep and waking—vaginal thermoconductance studies. Arch Sex Behav 12:97–122

Flaherty AW (2005) Frontotemporal and dopaminergic control of idea generation and creative drive. J Comp Neurol 493:147–153

Fogel SM, Smith CT (2011) The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35:1154–1165

Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, Morin CM (2012) Insomnia and daytime cognitive performance: a meta-analysis. Sleep Med Rev 16:83–94

Fosse MJ, Fosse R, Hobson JA, Stickgold RJ (2003) Dreaming and episodic memory: a functional dissociation? J Cogn Neurosci 15:1–9
Fosse R, Stickgold R, Hobson JA (2001) Brain-mind states: reciprocal variation in thoughts and hallucinations. Psychol Sci 12:30–36
Foulkes D (1993) Children's dreaming. In: Cavarello C, Foulkes D (eds) Dreaming as cognition. Harvester Wheatsheaf, New York, pp 114–132
Foulkes D (1996) Dream research: 1953–1993. Sleep 19:609–624
Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6:119–130
Freud S (1900) The interpretation of dreams. Macmillan, New York
Georgiadis JR, Reinders AA, Van der Graaf FH, Paans AM, Kortekaas R (2007) Brain activation during human male ejaculation revisited. NeuroReport 18:553–557
Gujar N, Yoo SS, Hu P, Walker MP (2011) Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. J Neurosci 31:4466–4474
Haber SN, Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35:4–26
Hanlon EC, Benca RM, Baldo BA, Kelley AE (2010) REM sleep deprivation produces a motivational deficit for food reward that is reversed by intra-accumbens amphetamine in rats. Brain Res Bull 83:245–254
Harris GC, Wimmer M, Aston-Jones G (2005) A role for lateral hypothalamic orexin neurons in reward seeking. Nature 437:556–559
Harrison Y, Horne JA (2000) The impact of sleep deprivation on decision making: a review. J Exp Psychol Appl 6:236–249
Hasler BP, Buysse DJ, Kupfer DJ, Germain A (2010) Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. Psychiatry Res 178:205–207
Hobson JA (2009) REM sleep and dreaming: towards a theory of protoconsciousness. Nat Rev Neurosci 10:803–813
Hobson JA, Pace-Schott EF, Stickgold R, Kahn D (1998) To dream or not to dream? Relevant data from new neuroimaging and electrophysiological studies. Curr Opin Neurobiol 8:239–244
Holstege G, Georgiadis JR (2004) The emotional brain: neural correlates of cat sexual behavior and human male ejaculation. Prog Brain Res 143:39–45
Holstege G, Huynh HK (2011) Brain circuits for mating behavior in cats and brain activations and de-activations during sexual stimulation and ejaculation and orgasm in humans. Horm Behav 59:702–707
Home J (1988) Sleep loss and "divergent" thinking ability. J Sleep Res Sleep Med 11:528–536
Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78–81
Inzelberg R (2013) The awakening of artistic creativity and Parkinson's disease. Behav Neurosci 127:256–261
Johnson EO, Roth T, Breslau N (2006) The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. J Psychiatr Res 40:700–708
Jouvet M (1965) Paradoxical sleep—a study of its nature and mechanisms. Prog Brain Res 18:20–62
Kahn-Greene ET, Killgore DB, Kamimori GH, Balkin TJ, Killgore WD (2007) The effects of sleep deprivation on symptoms of psychopathology in healthy adults. Sleep Med 8:215–221
Kamphuis J, Meerlo P, Koolhaas JM, Lancel M (2012) Poor sleep as a potential causal factor in aggression and violence. Sleep Med 13:327–334
Karacan I, Williams RL, Thornby JI, Salis PJ (1975) Sleep-related penile tumescence as a function of age. Am J Psychiatry 132:932–937
Killgore WD, Killgore DB, Day LM, Li C, Kamimori GH, Balkin TJ (2007) The effects of 53 hours of sleep deprivation on moral judgment. Sleep 30:345–352

Koukkou M, Lehmann D (1993) A model of dreaming and its functional significance: the state-shift hypothesis. In: Moffitt A, Kramer M, Hoffmann R (eds) The functions of dreaming (SUNY series in dream studies). State University of New York Press, New York, pp 51–118
Kulisevsky J, Pagonabarraga J, Martinez-Corral M (2009) Changes in artistic style and behaviour in Parkinson's disease: dopamine and creativity. J Neurol 256:816–819
Lamid S (1986) Nocturnal penile tumescence studies in spinal cord injured males. Paraplegia 24:26–31
Lansink CS, Goltstein PM, Lankelma JV, Joosten RN, McNaughton BL, Pennartz CM (2008) Preferential reactivation of motivationally relevant information in the ventral striatum. J Neurosci 28:6372–6382
Lansink CS, Goltstein PM, Lankelma JV, McNaughton BL, Pennartz CM (2009) Hippocampus leads ventral striatum in replay of place-reward information. PLoS Biol 7:e1000173
Lena I, Parrot S, Deschaux O, Muffat-Joly S, Sauvinet V, Renaud B, Suaud-Chagny MF, Gottesmann C (2005) Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J Neurosci Res 81:891–899
Limb CJ, Braun AR (2008) Neural substrates of spontaneous musical performance: an FMRI study of jazz improvisation. PLoS ONE 3:e1679
Lisman JE, Grace AA (2005) The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46:703–713
Luboshitzky R, Herer P, Levi M, Shen-Orr Z, Lavie P (1999) Relationship between rapid eye movement sleep and testosterone secretion in normal men. J Androl 20:731–737
Maloney KJ, Mainville L, Jones BE (2002) c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. Eur J Neurosci 15:774–778
Maquet P (2001) The role of sleep in learning and memory. Science 294:1048–1052
Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, Del Fiore G, Degueldre C, Meulemans T, Luxen A, Franck G, Van Der Linden M, Smith C, Cleeremans A (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3:831–836
Maquet P, Peters J, Aerts J, Delfiore G, Degueldre C, Luxen A, Franck G (1996) Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383:163–166
Maquet P, Ruby P, Maudoux A, Albouy G, Sterpenich V, Dang-Vu T, Desseilles M, Boly M, Perrin F, Peigneux P, Laureys S (2005) Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. Prog Brain Res 150:219–227
Maquet P, Schwartz S, Passingham R, Frith C (2003) Sleep-related consolidation of a visuomotor skill: brain mechanisms as assessed by functional magnetic resonance imaging. J Neurosci 23:1432–1440
Marshall L, Helgadottir H, Molle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613
Martinez-Gonzalez D, Obermeyer W, Fahy JL, Riboh M, Kalin NH, Benca RM (2004) REM sleep deprivation induces changes in coping responses that are not reversed by amphetamine. Sleep 27:609–617
Meerlo P, Koehl M, van der Borght K, Turek FW (2002) Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. J Neuroendocrinol 14:397–402
Meerlo P, Mistlberger RE, Jacobs BL, Heller HC, McGinty D (2009) New neurons in the adult brain: the role of sleep and consequences of sleep loss. Sleep Med Rev 13:187–194
Messinger D, Dondi M, Nelson-Goens GC, Beghi A, Fogel A, Simion F (2002) How sleeping neonates smile. Dev Sci 5:48–54
Messinger D, Fogel A (2007) The interactive development of social smiling. Adv Child Dev Behav 35:327–366
Mileykovskiy BY, Kiyashchenko LI, Siegel JM (2005) Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 46:787–798

Mirmiran M, Scholtens J, van de Poll NE, Uylings HB, van der Gugten J, Boer GJ (1983) Effects of experimental suppression of active (REM) sleep during early development upon adult brain and behavior in the rat. Brain Res 283:277–286

Nielsen T, Levin R (2007) Nightmares: a new neurocognitive model. Sleep Med Rev 11:295–310

Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, Price JC, Sembrat RC, Ombao H, Reynolds CF, Monk TH, Hall M, Kupfer DJ, Moore RY (2002) Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain 125:1105–1115

Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, Moore RY (1997) Forebrain activation in REM sleep: an FDG PET study. Brain Res 770:192–201

Oudiette D, De Cock VC, Lavault S, Leu S, Vidailhet M, Arnulf I (2009) Nonviolent elaborate behaviors may also occur in REM sleep behavior disorder. Neurology 72:551–557

Oudiette D, Dealberto MJ, Uguccioni G, Golmard JL, Merino-Andreu M, Tafti M, Garma L, Schwartz S, Arnulf I (2012) Dreaming without REM sleep. Conscious Cogn 21:1129–1140

Oudiette D, Paller KA (2013) Upgrading the sleeping brain with targeted memory reactivation. Trends Cogn Sci 17:142–149

Pace-Schott EF, Milad MR, Orr SP, Rauch SL, Stickgold R, Pitman RK (2009) Sleep promotes generalization of extinction of conditioned fear. Sleep 32:19–26

Pace-Schott EF, Nave G, Morgan A, Spencer RM (2012) Sleep-dependent modulation of affectively guided decision-making. J Sleep Res 21:30–39

Panksepp J (1998) Affective neuroscience: the foundations of human and animal emotions. Oxford University Press, New York

Payne JD, Kensinger EA (2010) Sleep leads to changes in the emotional memory trace: evidence from fMRI. J Cogn Neurosci 23:1285–1297

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44:535–545

Pennartz CM, Lee E, Verheul J, Lipa P, Barnes CA, McNaughton BL (2004) The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. J Neurosci 24:6446–6456

Perogamvros L (2012) Does primary narcissism exist in newborn babies? Evidence from sleep science. Front Psychol 3:330

Perogamvros L, Baud P, Hasler R, Cloninger CR, Schwartz S, Perrig S (2012) Active reward processing during human sleep: insights from sleep-related eating disorder. Front Neurol 3:168

Perogamvros L, Schwartz S (2012) The roles of the reward system in sleep and dreaming. Neurosci Biobehav Rev 36:1934–1951

Ponz A, Khatami R, Poryazova R, Werth E, Boesiger P, Bassetti CL, Schwartz S (2010a) Abnormal activity in reward brain circuits in human narcolepsy with cataplexy. Ann Neurol 67:190–200

Ponz A, Khatami R, Poryazova R, Werth E, Boesiger P, Schwartz S, Bassetti CL (2010b) Reduced amygdala activity during aversive conditioning in human narcolepsy. Ann Neurol 67:394–398

Popa D, Duvarci S, Popescu AT, Lena C, Pare D (2010) Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. Proc Natl Acad Sci U S A 107:6516–6519

Rasch B, Buchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315:1426–1429

Ravassard P, Pachoud B, Comte JC, Mejia-Perez C, Scote-Blachon C, Gay N, Claustrat B, Touret M, Luppi PH, Salin PA (2009) Paradoxical (REM) sleep deprivation causes a large and rapidly reversible decrease in long-term potentiation, synaptic transmission, glutamate receptor protein levels, and ERK/MAPK activation in the dorsal hippocampus. Sleep 32:227–240

Revonsuo A (2000) The reinterpretation of dreams: an evolutionary hypothesis of the function of dreaming. Behav Brain Sci 23:877–901; discussion 904–1121

Riemann D, Voderholzer U (2003) Primary insomnia: a risk factor to develop depression? J Affect Disord 76:255–259
Roane BM, Taylor DJ (2008) Adolescent insomnia as a risk factor for early adult depression and substance abuse. Sleep 31:1351–1356
Roffwarg HP, Muzio JN, Dement WC (1966) Ontogenetic development of the human sleep-dream cycle. Science 152:604–619
Rosanova M, Ulrich D (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25:9398–9405
Rudoy JD, Voss JL, Westerberg CE, Paller KA (2009) Strengthening individual memories by reactivating them during sleep. Science 326:1079
Schabus M, Dang-Vu TT, Albouy G, Balteau E, Boly M, Carrier J, Darsaud A, Degueldre C, Desseilles M, Gais S, Phillips C, Rauchs G, Schnakers C, Sterpenich V, Vandewalle G, Luxen A, Maquet P (2007) Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A 104:13164–13169
Schredl M (2010) Characteristics and contents of dreams. Int Rev Neurobiol 92:135–154
Schwartz S (2003) Are life episodes replayed during dreaming? Trends Cogn Sci 7:325–327
Schwartz S (2004) What dreaming can reveal about cognitive and brain functions during sleep: a lexico-statistical analysis of dream reports. Psychol Belgica 44:5–42
Schwartz S, Maquet P (2002) Sleep imaging and the neuro-psychological assessment of dreams. Trends Cogn Sci 6:23–30
Schwartz S, Maquet P, Frith C (2002) Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination. Proc Natl Acad Sci U S A 99:17137–17142
Schwartz S, Ponz A, Poryazova R, Werth E, Boesiger P, Khatami R, Bassetti CL (2008) Abnormal activity in hypothalamus and amygdala during humour processing in human narcolepsy with cataplexy. Brain 131:514–522
Shaffery JP, Sinton CM, Bissette G, Roffwarg HP, Marks GA (2002) Rapid eye movement sleep deprivation modifies expression of long-term potentiation in visual cortex of immature rats. Neuroscience 110:431–443
Smith MR, Antrobus JS, Gordon E, Tucker MA, Hirota Y, Wamsley EJ, Ross L, Doan T, Chaklader A, Emery RN (2004) Motivation and affect in REM sleep and the mentation reporting process. Conscious Cogn 13:501–511
Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A, Balteau E, Dang-Vu TT, Desseilles M, D'Argembeau A, Gais S, Rauchs G, Schabus M, Degueldre C, Luxen A, Collette F, Maquet P (2007) Sleep-related hippocampo-cortical interplay during emotional memory recollection. PLoS Biol 5:e282
Sterpenich V, Albouy G, Darsaud A, Schmidt C, Vandewalle G, Dang Vu TT, Desseilles M, Phillips C, Degueldre C, Balteau E, Collette F, Luxen A, Maquet P (2009) Sleep promotes the neural reorganization of remote emotional memory. J Neurosci 29: 5143-52
Stephenson KM, Schroder CM, Bertschy G, Bourgin P (2012). Complex interaction of circadian and non-circadian effects of light on mood: Shedding new light on an old story. Sleep Med Rev 16:445–454
Stickgold R (2005) Sleep-dependent memory consolidation. Nature 437:1272–1278
Stickgold R, Scott L, Rittenhouse C, Hobson JA (1999) Sleep-induced changes in associative memory. J Cogn Neurosci 11:182–193
Strauch I, Meier B (1996) In search of dreams: results of experimental dream research. State University of New York Press, New York
Takahashi K, Lin JS, Sakai K (2008) Neuronal activity of orexin and non-orexin waking-active neurons during wake-sleep states in the mouse. Neuroscience 153:860–870
Takenouchi K, Nishijo H, Uwano T, Tamura R, Takigawa M, Ono T (1999) Emotional and behavioral correlates of the anterior cingulate cortex during associative learning in rats. Neuroscience 93:1271–1287
Takeuchi H, Taki Y, Sassa Y, Hashizume H, Sekiguchi A, Fukushima A, Kawashima R (2010) Regional gray matter volume of dopaminergic system associate with creativity: evidence from voxel-based morphometry. NeuroImage 51:578–585

Thompson JL, Borgland SL (2011) A role for hypocretin/orexin in motivation. Behav Brain Res 217:446–453
Valli K, Revonsuo A (2009) The threat simulation theory in light of recent empirical evidence: a review. Am J Psychol 122:17–38
Valli K, Revonsuo A, Palkas O, Ismail KH, Ali KJ, Punamaki RL (2005) The threat simulation theory of the evolutionary function of dreaming: evidence from dreams of traumatized children. Conscious Cogn 14:188–218
Van Dongen HP, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26:117–126
Venkatraman V, Chuah YM, Huettel SA, Chee MW (2007) Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. Sleep 30:603–609
Venkatraman V, Huettel SA, Chuah LY, Payne JW, Chee MW (2011) Sleep deprivation biases the neural mechanisms underlying economic preferences. J Neurosci 31:3712–3718
Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Logan J, Benveniste H, Kim R, Thanos PK, Ferre S (2012) Evidence That sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. J Neurosci 32:6711–6717
Wagner U, Gais S, Born J (2001) Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem 8:112–119
Wagner U, Gais S, Haider H, Verleger R, Born J (2004) Sleep inspires insight. Nature 427:352–355
Walker MP (2010) Sleep, memory and emotion. Prog Brain Res 185:49–68
Walker MP, Liston C, Hobson JA, Stickgold R (2002) Cognitive flexibility across the sleep-wake cycle: REM-sleep enhancement of anagram problem solving. Brain Res Cogn Brain Res 14:317–324
Walker MP, van der Helm E (2009) Overnight therapy? The role of sleep in emotional brain processing. Psychol Bull 135:731–748
Wang SH, Morris RG (2010) Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation. Annu Rev Psychol 61(49–79):C1–C4
Waterhouse J, Nevill A, Finnegan J, Williams P, Edwards B, Kao SY, Reilly T (2005) Further assessments of the relationship between jet lag and some of its symptoms. Chronobiol Int 22:121–136
Weisman O, Magori-Cohen R, Louzoun Y, Eidelman AI, Feldman R (2011) Sleep-wake transitions in premature neonates predict early development. Pediatrics 128:706–714
Wilhelm I, Diekelmann S, Molzow I, Ayoub A, Molle M, Born J (2011) Sleep selectively enhances memory expected to be of future relevance. J Neurosci 31:1563–1569
Winson J (1972) Interspecies differences in the occurrence of theta. Behav Biol 7:479–487
Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP (2007) The human emotional brain without sleep–a prefrontal amygdala disconnect. Curr Biol 17:R877–R878
Zohar D, Tzischinsky O, Epstein R, Lavie P (2005) The effects of sleep loss on medical residents' emotional reactions to work events: a cognitive-energy model. Sleep 28:47–54

Sleep and Plasticity in Schizophrenia

Kate E. Sprecher, Fabio Ferrarelli and Ruth M. Benca

Abstract Schizophrenia is a devastating mental illness with a worldwide prevalence of approximately 1 %. Although the clinical features of the disorder were described over one hundred years ago, its neurobiology is still largely elusive despite several decades of research. Schizophrenia is associated with marked sleep disturbances and memory impairment. Above and beyond altered sleep architecture, sleep rhythms including slow waves and spindles are disrupted in schizophrenia. In the healthy brain, these rhythms reflect and participate in plastic processes during sleep. This chapter discusses evidence that schizophrenia patients exhibit dysfunction of sleep-mediated plasticity on a behavioral, cellular, and molecular level and offers suggestions on how the study of sleeping brain activity can shed light on the pathophysiological mechanisms of the disorder.

Keywords Sleep · Schizophrenia · Plasticity · EEG · Thalamocortical circuits

Contents

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1 Introduction

Schizophrenia is a chronic mental illness, characterized by psychosis and other symptoms that result in significant cognitive, social, and occupational dysfunction. The lifetime prevalence of schizophrenia has been estimated at about 1 % of the population worldwide, with males and females equally affected. In addition to its positive (e.g., hallucinations, delusions) and negative (e.g., apathy, anhedonia) symptoms, schizophrenia is associated with marked sleep disturbances and cognitive deficits. Because diagnosis is based solely on clinical criteria, it is likely that schizophrenia is not a single disease entity but rather may include a group of disorders resulting in similar clinical symptomatology. Sleep may be of particular relevance to schizophrenia, since abnormal brain connectivity and plasticity are thought to be core pathological features of the disorder and both are reflected in the sleep electroencephalogram (EEG) (Stephan et al. 2006). Furthermore, electrophysiological measurements during sleep eliminate many factors that confound waking assessments of brain activity and cognition, including movement, attention, motivation, and comprehension of instructions. Consequently, sleep provides a unique modality for investigating neuropathological mechanisms, biological markers, and therapeutic targets for schizophrenia. This chapter discusses the evidence that schizophrenia patients exhibit dysfunction of sleep-mediated plasticity on a behavioral, cellular, and molecular level and offers suggestions on how further study of sleeping brain activity can shed light on the pathophysiological mechanisms of the disorder.

2 Description of the Disorder

Schizophrenia tends to appear in late adolescence or early adulthood, with earlier onset in men than in women. Diagnosis of schizophrenia is based on the presence of two or more characteristic positive and negative symptoms that persist for at least

Table 1 Diagnostic criteria for schizophrenia. Adapted from DSM-5, the American Psychiatric Association (2013)

Two or more of the following present for at least one month (less if treated)
Positive symptoms (at least one)
• Delusions
• Hallucinations
• Disorganized speaking and thinking
• Disorganized or catatonic behavior
Negative symptoms
• Affective flattening
• Diminished fluency and productivity of thought and speech (alogia)
• Lack of motivation (avolition)
Other criteria
Continuous signs of disturbance for at least 6 months
Social/occupational dysfunction in work, self-care, or interpersonal relationships

1 month, in conjunction with significant dysfunction in work, interpersonal relations and/or self-care, and continuous signs of illness that are present for at least 6 months (DSM V, (American Psychiatric Association 2013). Diagnostic criteria are summarized in Table 1. The vast majority of individuals afflicted with the disorder remain at least partially ill, with either a stable course or progressive deterioration; full remission is uncommon. Schizophrenia is associated with a 10- to 25-year reduction in life expectancy; this is related both to elevated rates of suicides and accidents, which are closely associated with the illness itself, and higher rates of medical disorders (e.g., cardiovascular disease and cancer), which are related to comorbid factors such as increased substance use, poor diet, side effects of antipsychotic medications, and suboptimal medical care (Laursen et al. 2012).

Whereas the clinical features of schizophrenia have been described for over one hundred years (Bleuler 1911), the neurobiology of the disorder is still largely elusive despite decades of research. A large body of evidence now exists identifying biological abnormalities that characterize schizophrenia and many competing theories have been put forward to explain the pathophysiological mechanisms that might explain these observations (MacDonald and Schulz 2009). Some key theories are summarized in Table 2. A number of studies indicate that abnormalities in neurotransmitter pathways, gray and white matter structures, and cortical circuits that are involved in both sleep and brain plasticity may underlie specific symptoms and neurocognitive deficits in schizophrenia. Dysfunction of thalamocortical circuits is of particular interest, as these connections are thought to play a central role in coordinating sleep-mediated plasticity.

Table 2 Biological hypotheses of schizophrenia

Description	Selected reviews	Relevance to sleep and plasticity
Neurodevelopmental hypothesis		
Disturbances during critical periods of brain development results in lesions that produce the symptoms of schizophrenia. Disturbances could result from genetic or environmental factors.	Fatemi and Folsom (2009), Rapoport et al. (2012)	• Slow waves and spindles reflect and participate in cortical maturation • Slow wave and spindle deficits may indicate aberrant neural development • Disruption of thalamocortical system during development would lead to impaired slow wave- and spindle-mediated plasticity
Dysconnection hypothesis		
Abnormal modulatory activity of neurotransmitters including DA, ACh, and 5-HT results in altered regulation of NMDA-receptor-mediated plasticity. The resulting abnormal functional integration between brain regions gives rise to symptoms of schizophrenia.	Stephan et al. (2009)	• NMDAR inactivation may disrupt thalamocortical oscillations, leading to spindle and slow wave deficits that would impact sleep-dependent memory processes
Dopamine hypothesis		
Multiple environmental and genetic factors lead to increased presynaptic striatal dopaminergic function. Dysregulation of dopamine-driven circuits of stimulus salience and reward lead to the positive and negative symptoms of schizophrenia.	Howes and Kapur (2009)	• D4 receptor excess could disrupt circadian signaling and thalamocortical oscillations • COMT SNP shows impaired memory and altered responses to sleep-suppressing agents
NMDAR hypofunction hypothesis		
NMDAR antagonists produce schizophrenia-like symptoms in humans and animals, leading to the hypothesis that NMDAR hypofunction is a core pathological mechanism of schizophrenia. This hypofunction impacts other neurotransmitter systems and may result from genetic and non-genetic factors early in life.	Gilmour et al. (2012), Olney et al. (1999)	• Hypofunction of NMDARs on TRN neurons would reduce reticular inhibition of thalamocortical neurons and lead to cortical hyperactivity, giving rise to disrupted plasticity and psychotic symptoms
Genetic hypotheses		
A single genetic cause of schizophrenia is unlikely. Genetic hypotheses propose polygenic inheritance patterns, post-fertilization mutations due to genetic or epigenetic factors, or some combination of these.	Kim et al. (2011), Owen (2012)	• COMT regulates DA levels, which impact sleep-dependent plasticity in the PFC and TRN • Flies expressing DISC1 show altered sleep duration. During neurodevelopment, DISC1 is expressed in the TRN, which generates sleep spindles

ACh acetylcholine; *COMT SNP* catechol-o-methyl transferase single nucleotide polymorphism; *DISC-1* disrupted-in-schizophrenia-1; *DA* dopamine; *5-HT* serotonin; *NMDAR* N-methyl-D-aspartate receptor; *PFC* prefrontal cortex; *TRN* thalamic reticular nucleus

2.1 Sleep Patterns in Schizophrenia

After the neurophysiological identification of rapid eye movement (REM) sleep in the early 1950s, schizophrenia was one of the first disorders to be studied using polysomnography, motivated by the apparent similarities between dreaming and the positive symptoms of schizophrenia (hallucinations, delusions). Although schizophrenia did not turn out to be a disorder of REM sleep intrusion into wakefulness (Dement 1955; Rechtschaffen et al. 1964), sleep disturbance can be a significant clinical symptom and objective sleep EEG abnormalities have been identified across numerous studies. During periods of acute psychosis, sleep is often severely affected, with profound insomnia, reduced total sleep time, and fragmented sleep. In terms of sleep architecture, sleep recordings in schizophrenic patients have fairly consistently documented objective evidence of insomnia, including prolonged latency to sleep, reduced sleep efficiency, and reduced total sleep amount (Benca et al. 1992; Chouinard et al. 2004). Decrements in the amounts of visually scored deep stage 3 sleep (N3), also called slow wave sleep (SWS), have also been reported in some (Hiatt et al. 1985; Keshavan et al. 1998; Sekimoto et al. 2007; Zarcone et al. 1987), but not in all studies (Kempenaers et al. 1988; Lauer et al. 1997; Tandon et al. 1992). REM sleep abnormalities in schizophrenia have not been demonstrated consistently, although a number of early studies suggested that schizophrenics, like patients with mood disorders, had reduced latency to REM sleep (Kupfer et al. 1970). However, several meta-analyses have failed to support any consistent changes in latency to REM sleep or REM sleep amounts (Benca et al. 1992; Chouinard et al. 2004).

2.2 Memory Deficits in Schizophrenia

One of the most debilitating manifestations of disrupted brain plasticity in schizophrenia is impaired memory in several domains. Verbal declarative memory deficits are the most consistently found impairments in schizophrenia, confirmed by several meta-analyses (Cirillo and Seidman 2003; Sitskoorn et al. 2004; Snitz et al. 2006). Verbal declarative memory is memory for facts, ideas, stories, or events that can be consciously recalled. Impairments are present throughout the course of the illness, and in high-risk subjects and non-psychotic relatives of individuals with schizophrenia, suggesting that these deficits are partly associated with a genetic vulnerability to the disorder (Gur et al. 2007; Sitskoorn et al. 2004). Working memory is the 'scratch pad of the mind,' used for holding and manipulating information online during a cognitive task (Baddeley 1992). Schizophrenia patients have impaired working memory (Horan et al. 2008) and in unaffected offspring reduced performance predicted the later development of psychosis (Erlenmeyer-Kimling et al. 2000). Procedural learning is non-declarative memory for the performance of perceptual or motor tasks. Most studies report normal procedural

learning in schizophrenia patients (Clare et al. 1993; Weickert 2002). However, these reports were derived from testing within a single session. Since healthy individuals show improvement in procedural memory after a night of sleep, Manoach et al. (2004) investigated the influence of sleep on learning in patients with schizophrenia. Despite normal learning within a training session, schizophrenics failed to show an improvement after a night of sleep, in contrast to healthy individuals, indicating a failure of sleep-mediated procedural memory consolidation in schizophrenia.

3 Neurochemical Abnormalities and Sleep-Dependent Plasticity

Neurotransmitter systems implicated in the pathogenesis of schizophrenia include dopamine, gamma-aminobutyric acid (GABA), acetylcholine, glutamate, and neuromodulators such as melatonin and orexin. These systems play important roles in neuroplasticity. Furthermore, sleep–wake regulation is achieved through a complex interaction of neurotransmitters in distributed brain regions; thus, abnormalities in these systems in schizophrenia are likely to impinge upon sleep and sleep-related plasticity.

3.1 Dopamine

Numerous studies show that dopamine (DA) neurotransmission is reduced in the cortex and elevated in the striatum in schizophrenia (Abi-Dargham et al. 2012; Fusar-Poli and Meyer-Lindenberg 2013; Howes et al. 2012). Dopaminergic circuits regulate both neuroplasticity and sleep–wake cycles. DA is a powerful modulator of synaptic plasticity via complex signaling that varies by receptor type and neural circuit. DA exerts its effects via G-protein-coupled receptors that may be excitatory (D1) or inhibitory (D2), with downstream effects on membrane excitability, synaptic transmission, protein trafficking, and gene transcription (Tritsch and Sabatini 2012). DA promotes wake and suppresses REM and non-REM (NREM) sleep, acting through projections from the ventral tegmental area, substantia nigra pars compacta, and ventral periaqueductal gray matter to inhibit sleep-promoting neurons in the basal forebrain, midbrain, brainstem, and hypothalamus (Monti and Jantos 2008). Although the impact of DA dysfunction on sleep-dependent plasticity has not yet been examined in schizophrenia, several lines of evidence suggest that it deserves further attention.

Firstly, the efficacy of the psychostimulant modafinil and its effects on sleep EEG are modulated by the presence of a polymorphism in the catechol-o-methyl transferase (COMT) gene, which is more common in schizophrenia patients than in

the general population (Bodenmann et al. 2009; Bodenmann and Landolt 2010). COMT is an enzyme that degrades dopamine, and the polymorphism predicts reduced cognitive performance (Weinberger et al. 2001). The genotype's interaction with modafinil suggests that COMT may play a role in altered sleep–wake regulation in schizophrenia. Secondly, elevated levels of D4 receptors (members of the D2-like receptor family) have been reported in schizophrenia (Seeman et al. 1993). D4 receptors are present in the pineal gland, where they decrease melatonin release through binding of adrenergic receptors. The pineal gland regulates sleep–wake rhythms through the circadian release of melatonin; therefore, the increase of D4 receptors in schizophrenia could contribute to the irregular sleep–wake patterns observed in the disorder (González et al. 2012). Moreover, the thalamic reticular nucleus (TRN), the structure responsible for generating sleep spindles, is rich in D4 receptors. D4 receptors are present presynaptically on GABA-containing projections from the globus pallidus to the TRN (Gandia et al. 1993; García-Cabezas et al. 2007), and activation of the D4 receptors reduces GABA release onto the TRN (Govindaiah et al. 2010). Thus, an excess of D4 receptors in schizophrenia could disrupt TRN control of thalamocortical oscillations, which coordinate sleep-related plasticity. However, the origins of these projections and the effects of dopamine on TRN neurons are still controversial (Florán et al. 2004; Mrzljak et al. 1996). Finally, in schizophrenia patients, working memory impairment correlates with increased D1-receptor binding potential in prefrontal cortex, suggesting a compensatory upregulation of the receptor in response to cortical DA deficiencies (Abi-Dargham et al. 2002). Animal studies suggest that prefrontal D1 receptors sustain the activity of prefrontal neurons while a stimulus is held in memory, and this persistent activity is considered the neural correlate of working memory (Gao et al. 2001). At first glance, working memory might be considered a purely waking function; however, working memory performance is improved by prior sleep (Kuriyama et al. 2008) and impaired by sleep deprivation (Drummond et al. 2012; Hagewoud et al. 2010). Sleep may therefore be a useful tool for probing abnormal DA function and working memory in schizophrenia.

3.2 Acetylcholine

Reduced cholinergic activity and abnormal cholinergic transmission have been found consistently in schizophrenia (Crook et al. 2000; 2001; Raedler et al. 2003) and are related to cognitive symptoms in animal models (Sarter et al. 2012). Although acetylcholine (ACh) is excitatory, AChRs are located both pre- and postsynaptically, allowing for a complex role in fine-tuning neuronal excitability (Drever et al. 2011). ACh can both facilitate and inhibit long-term potentiation (LTP) through graded effects on the responsiveness of glutamatergic and GABAergic cells in the hippocampus that mediate memory formation (Drever et al. 2011) and DA neurons in the ventral tegmental area that mediate reward and addiction (Gao et al. 2001). ACh also supports longer-term changes in cortical circuits by promoting

synchronous cortical and subcortical firing; this may facilitate long-term plasticity by increasing the baseline excitability of neurons, which are then more responsive to modulation by other transmitters (Picciotto et al. 2012). Cholinergic transmission in the brainstem is important for the initiation and coordination of REM sleep (Jones 2005; Marks and Birabil 1998). Administration of muscarinic agonists induces shorter REM latencies in healthy individuals. In schizophrenia patients, the effect is much more pronounced than in healthy controls, suggesting a muscarinic cholinergic supersensitivity in the disease (Riemann et al. 1994). Cholinergic tone is normally high during REM sleep and low during NREM sleep, and in healthy young men, pharmacologically lowering REM cholinergic tone impairs consolidation of motor memory (Rasch et al. 2009), while pharmacologically elevating NREM ACh tone impairs consolidation of verbal declarative memory (Gais and Born 2004). Therefore, the contribution of ACh dysfunction to impaired sleep-dependent memory in schizophrenia warrants further investigation.

3.3 Glutamate

Glutamate is the most prevalent excitatory neurotransmitter in the central nervous system, and dysfunctions of glutamatergic neurotransmission are hypothesized to be an important mechanism of schizophrenia pathophysiology (Table 2). In particular, abnormalities in the N-methyl-D-aspartate receptor (NMDAR), a glutamate-gated ion channel, are thought to contribute to disrupted synaptic plasticity in the disorder (Marsman et al. 2013). Multiple signaling pathways modulating sleep and synaptic plasticity converge on the NMDA receptor, for example, D1 agonists and D2 antagonists increase NMDAR-dependent LTP, whereas D2 agonists decrease LTP (Centonze et al. 2004; Tseng and O'Donnell 2004) and acetylcholine modulates NMDA-dependent LTP and long-term depression (LTD) in visual cortex (Kirkwood et al. 1999) and hippocampus (Yun et al. 2000). In mice, sleep deprivation altered the ratio between LTP and LTD, a key cellular mechanism of neural plasticity, and changed the subunit composition of NMDARs (Kopp et al. 2006). Low doses of NMDAR antagonists produce arousal, while high doses produce sedation (Siegel 2011). Ketamine, a NMDAR antagonist that induces schizophrenia-like symptoms, disrupts thalamocortical rhythmicity (Buzsáki 1991), which is important for sleep-dependent memory processes. The role of the thalamocortical system in sleep-dependent plasticity is discussed in further detail below.

4 Structural and Functional Abnormalities

Gray matter atrophy and disrupted white matter connectivity have been reported consistently in schizophrenia, especially in frontal and temporal areas and in thalamocortical networks, including the thalamic radiation which carries fibers from

the thalamus to prefrontal areas (Borgwardt et al. 2008; Gaser et al. 2004; Heinrichs and Zakzanis 1998; Kawada et al. 2009; Kyriakopoulos and Frangou 2009; McIntosh et al. 2008; Nuechterlein 1983; Ren et al. 2013; Snitz et al. 2006). Functional magnetic resonance imaging (fMRI) has revealed abnormal patterns of activity in the default mode network, a highly interconnected brain system that subserves self-referential thought and interpretation of the external environment (Hasenkamp et al. 2011; Ren et al. 2013; Skudlarski et al. 2010). These findings are in keeping with the view that disordered brain connectivity is central to schizophrenia (Stephan et al. 2006) (Table 2). Interestingly, the functional findings did not co-localize with anatomical abnormalities in gray or white matter in the same subjects. Abnormal functional connectivity may reflect reorganization of functional networks in response to declining structural connections. Sleep EEG patterns reflect propagation of neural activity through structural and functional networks; therefore, the use of EEG systems with high spatial resolution could further characterize the relationship between altered anatomical and functional connectivity in schizophrenia. An advantage of EEG recordings is the ability to monitor activity on a timescale closer to neuronal signaling (milliseconds) than fMRI (seconds). For example, by performing source modeling analysis of scalp-recorded EEG slow waves, it is possible to track the origin and propagation of slow waves along a mesial cortical highway, and the propagation of this wave is thought to play a role in coordinating neuronal plastic activity (Massimini et al. 2004). This technique has yet to be applied to schizophrenia.

In task-related studies of schizophrenia, abnormal prefrontal cortical activation is the most established finding, often associated with impaired performance in cognitive paradigms involving working memory (Barch et al. 2012), reinforcement learning (Ragland et al. 2012), and executive functions (Carter et al. 2012). Increased prefrontal activity in schizophrenia patients has been interpreted as a failure of automation, the shift from controlled effortful cognitive performance to less attention-demanding strategies. Automation has been proposed to be accomplished by a system-level reorganization of memory traces during sleep, a process reflected in EEG waveforms including spindles and slow waves (Manoach and Stickgold 2009). Therefore, investigating sleep EEG in conjunction with learning tasks could shed light on the biological basis of dysfunctional memory processes in schizophrenia.

5 Genetic Factors

A strong familial risk for schizophrenia has long been recognized, and a meta-analysis of twin studies calculated that 80 % of the probability of developing schizophrenia could be attributed to genetic factors (Sullivan et al. 2003). Over 50 candidate genes have been identified, yet no gene or genetic factor is shared by all schizophrenia patients. Recent genome-wide association studies have found an increased frequency of single nucleotide polymorphisms (SNPs) in schizophrenia

(Lee et al. 2012). SNPs are the most common form of genetic variation within the general population and are therefore not unique to schizophrenia. However, SNPs may confer additional risk on individuals already predisposed to the illness. Their increased incidence in schizophrenia may explain the complex and heterogeneous phenotypes encountered in the disorder, and support a polygenic inheritance pattern. One SNP associated with schizophrenia is a functional polymorphism in the COMT gene (Cross-Disorder Group of the Psychiatric Genomics Consortium et al. 2013). As described earlier, COMT is an enzyme that regulates extracellular dopamine concentration in prefrontal cortex and the polymorphism leads to dopamine deficiency, which could impair sleep-dependent plasticity via altered oscillatory activity in the prefrontal cortex and thalamic reticular nucleus. Indeed, lower performance on working memory and prefrontal executive tasks is predicted by the presence of the COMT val allele in healthy controls, schizophrenia patients, and relatives of patients (Weinberger et al. 2001). The COMT SNP also influences sleep–wake regulation. Specifically, carriers of the val allele required a much lower dose of the stimulant modafinil to maintain attention during sleep deprivation (Bodenmann et al. 2009). Non-schizophrenia subjects with the val/val variant showed increased EEG activity in the high slow wave range (3.0–6.75 Hz) and the beta range (>16.75 Hz) during recovery sleep following modafinil treatment (Bodenmann and Landolt 2010). The ability of the COMT SNP to explain phenotypic variation in sleep architecture and EEG has not yet been explored in schizophrenia.

A well-researched gene consistently associated with schizophrenia is disrupted-in-schizophrenia 1 (DISC1), which encodes a multifunctional scaffold protein. It is implicated in neuronal migration and maturation during development, as well as in synaptic plasticity in the adult brain (Chubb et al. 2008). DISC1 also impacts sleep; transgenic flies expressing human DISC1 displayed increased duration of sleep bouts but normal circadian rhythms, suggesting a role for DISC1 in regulating sleep homeostasis (Sawamura et al. 2008). In the mouse brain, DISC1 is expressed only in some brain structures, including regions important for sleep and plasticity such as the hippocampus, parts of the neocortex, hyphothalamus, stria terminalis, and TRN. Furthermore, DISC1 is highly expressed in the TRN during development, in a period when thalamocortical connections take shape (Austin et al. 2004). Given their crucial role in sleep-dependent plasticity, abnormal development of thalamocortical circuits would have far-reaching effects on sleep and cognition, in keeping with the view of schizophrenia as a neurodevelopmental disorder.

6 Sleep-Specific EEG Rhythms in Schizophrenia

Whereas early studies of sleep in schizophrenia focused on visually scored sleep architecture in 30-s epochs, modern automated analyses allow a more detailed assessment of sleep-specific rhythms by measuring power density and waveform counts. High-density EEG recordings from 256 channels, as opposed to 6 or less in

conventional polysomnography, afford sufficient spatial resolution to examine regional variation. Slow waves and spindles, the characteristic waveforms of NREM sleep, play important roles in neuroplasticity and have been studied extensively in schizophrenia. Interestingly, intracortical recordings in humans have shown that rather than being global brain phenomena, both slow waves and spindles can occur in local circuits as temporally and spatially independent phenomena (Nir et al. 2011). Furthermore, localized, use-dependent changes suggest that spindles and slow waves reflect the ability of local circuits to be plastic (Fisher and Vyazovskiy 2014; Goel et al. 2014; Huber et al. 2004). Therefore, sleep EEG could provide a powerful tool for testing the functionality of distinct circuits in schizophrenia.

6.1 Slow Wave Abnormalities in Schizophrenia

During the deepest stage of NREM sleep, the EEG is dominated by large slow waves in the delta frequency range (0.5–4 Hz) as detailed in Chap. 1 of this volume. At the cellular level, slow waves reflect synchronized transitions in large populations of cortical pyramidal neurons between a depolarized upstate (a state of increased firing) and a hyperpolarized downstate (a state of decreased firing) (Steriade et al. 1993). This slow oscillation is cortically generated and maintained (Amzica and Steriade 1995; Timofeev et al. 2000), but is shaped by the thalamus (Steriade et al. 1993). High-density EEG recordings show that cortical slow waves typically originate in frontal regions (the insula and cingulate gyrus) and travel in an anterior–posterior direction along the cingulate gyrus and neighboring regions (Murphy et al. 2009). This coincides with a major white fiber pathway identified by diffusion spectrum imaging (DSI) (Hagmann et al. 2008). Studies of sleep and learning demonstrate that slow waves reflect plastic changes. For example, when sleep was recorded following training on a visuomotor task, the cortex showed an increase in slow wave activity in task-relevant areas, which correlated with improved task performance the following morning (Huber et al. 2004). SWS also positively correlated with overnight improvement on tests of visual (Stickgold et al. 2000) and verbal declarative memory (Plihal and Born 1997). Moreover, selectively suppressing slow waves without shortening sleep time was detrimental to motor sequence learning (Landsness et al. 2011).

Slow wave deficits in schizophrenia have been frequently but inconsistently reported. Several studies have found that patients spend less time in visually scored stage N3. Automated analyses showed reduced power in the slow wave frequency range (0.5–4 Hz) and a lower count of slow waves across the total sleep period (Keshavan et al. 1998; Sekimoto et al. 2007). Differences in slow wave topography have also been reported. Whereas healthy controls showed significantly higher slow wave counts in right frontal and central regions, this asymmetry was lacking in patients with schizophrenia (Sekimoto et al. 2011). Slow wave deficits have been reported in medicated (Göder et al. 2004; Sekimoto et al. 2007), unmedicated

(Feinberg et al. 1969), first-episode neuroleptic naïve (Poulin et al. 2003), and remitted (Kupfer et al. 1970; Traub 1972) patients. Furthermore, a reduced slow wave count has been identified in non-psychotic first-degree relatives of schizophrenia patients, suggesting it may be a trait linked to predisposition to the disease (Keshavan et al. 2004). However, a number of studies have found no deficits in visually scored N3 or in automated measures of slow wave incidence, amplitude, or slope in medicated patients (Ferrarelli et al. 2010a; Manoach et al. 2010), or neuroleptic naïve patients (Forest et al. 2007). A meta-analysis of unmedicated patients also failed to confirm abnormalities in SWS as a percentage of total sleep time in schizophrenics (Chouinard et al. 2004). Inconsistencies between reports could be due to factors including sample size, medication status, and methodological differences such as slow wave detection algorithms. Alternatively, given the heterogeneous nature of the disorder, it may be that slow wave deficits are present only in a subset of schizophrenic patients.

Göder et al. (2004) examined the relationship between SWS and plasticity in chronically medicated schizophrenia patients and healthy controls matched for age, sex, and education level. Compared to controls, patients exhibited significantly shorter SWS duration and poorer visuospatial memory performance. SWS duration was positively correlated with memory performance in patients but not in controls (the lack of correlation in controls may have been due to a ceiling effect on performance). A subsequent study found that greater SWS duration was associated with better verbal declarative memory the following morning in chronically medicated schizophrenia patients (Göder et al. 2008). Furthermore, enhancing slow waves using transcranial direct current stimulation during NREM sleep improved verbal memory retention in medicated schizophrenia patients (Göder et al. 2013). These studies establish that the correlation of SWS with memory performance that was previously demonstrated in healthy individuals is also present in schizophrenia patients. Furthermore, reduced SWS in the disorder correlates with reduced cognitive performance, suggesting that in schizophrenia, learning deficits may be related to dysfunction in SWS-mediated plasticity. The studies described above relied on visually scored measures of SWS. Automated analyses that may be useful in future are the slope and amplitude of slow waves, which reflect synaptic strength (Esser et al. 2007; Vyazovskiy et al. 2009). Such measures could provide more detailed insight into the mechanism by which slow wave deficits contribute to impaired learning in schizophrenia.

Slow wave power is high at birth, increases steeply in the first few years of life, and then decreases dramatically during adolescence (Buchmann et al. 2011; Feinberg and Campbell 2010; Tarokh and Carskadon 2010). This inverted u-shaped pattern parallels other markers of neural development throughout childhood and adolescence, including synaptic density (Huttenlocher and Dabholkar 1997), the size of pyramidal neurons and the size and complexity of dendritic trees in prefrontal cortex (Petanjek et al. 2008), brain energy consumption measured by PET (Chugani et al. 1987), and microstructure of white matter tracts measured by diffusion tensor imaging (DTI) (Lebel et al. 2012). Healthy cortical maturation appears to follow a general pattern of early overproliferation followed by elimination, with

adolescence being a critical period of reorganization (Feinberg and Campbell 2010). Gray matter matures in a regionally and temporally complex pattern (Gogtay et al. 2004) and a recent cross-sectional study demonstrated that healthy developmental declines in SWA were correlated with gray matter maturation in a regionally specific manner (Buchmann et al. 2011). A longitudinal study of gray matter volumes in early-onset schizophrenia has shown accelerated gray matter losses during adolescence that correlated with symptom severity (Thompson et al. 2001). The dramatic decline in slow wave activity during adolescence likely reflects a reduction in synaptic strength and in the number of neurons available to participate in the synchronous slow oscillation. Given that slow wave amplitude depends on the ability of cortical neuronal populations to fire synchronously (Vyazovskiy et al. 2009), impaired neuronal integration could result in less coordinated activity, detectable as slow wave deficits. The reduction in slow waves seen in adults with schizophrenia may therefore be a product of disrupted neurodevelopment. The relationship between gray matter development and slow wave activity has not yet been examined in schizophrenia patients, however. Beyond being a marker of cortical maturation, slow waves may actively participate in the pruning of synapses (Maret et al. 2011). Neural proliferation and pruning during adolescence is a critical period for integrating complex neural circuits, and errors during this process would have severe cognitive and neural consequences.

6.2 Spindle Abnormalities in Schizophrenia

Sleep spindles are characteristic of NREM sleep and define stage N2. Spindles are waxing and waning bursts of highly synchronized 12–16 Hz oscillations, generated in the TRN and propagated throughout the cortex (Steriade 2003). In healthy humans and animals, an increase in the number and duration of spindles correlates with overnight improvements in declarative and procedural memory (Fogel and Smith 2011). Neuroimaging studies using simultaneous functional MRI and EEG showed that networks subserving memory function were activated during spindle activity, including thalamus, hippocampus, midbrain, anterior cingulate, and prefrontal cortex (Schabus et al. 2007), and spindle amplitude correlated with activity in the putamen and with gains in performance on a motor task (Doyon et al. 2011).

Several studies have found marked deficits in spindle activity in schizophrenia. Older studies using small sample sizes, manual techniques, and only 2 EEG leads (C3 and C4) had inconsistent spindle findings (Hiatt et al. 1985; Poulin et al. 2003; Van Cauter et al. 1991). Recent studies using automated detection methods, larger sample sizes, and more electrodes show more consistent deficits in schizophrenia. In the most comprehensive studies to date, medicated schizophrenia patients exhibited deficits in several spindle parameters compared to healthy controls, including power in the spindle range (13.75–15 Hz), spindle amplitude, duration, number, density (spindles/minute), and integrated spindle activity (ISA, calculated by integrating spindle activity over time) (Ferrarelli et al. 2007, 2010a).

Furthermore, the spindle deficits were not present in non-schizophrenia patients receiving antipsychotics, including major depressive and bipolar patients; therefore, the effect is not explained by medication, not found in patients with other psychiatric disorders, and could be specific to the disorder. ISA was inversely correlated with positive symptoms and distinguished schizophrenia patients from psychiatric and healthy controls; therefore, spindle parameters could be a useful biological marker for schizophrenia (Ferrarelli 2013).

Given the role of spindles in learning and memory, spindle deficits could be expected to correlate with cognitive impairment in schizophrenia. Indeed, Göder et al. (2008) found that in chronically medicated patients, greater spindle density was associated with better verbal declarative memory the following morning. The study did not include a non-schizophrenia control group as it was investigating the effect of olanzapine treatment. Wamsley et al. (2012) later tested the question directly. Compared to healthy controls, medicated patients with chronic schizophrenia showed less overnight improvement on a finger tapping motor task. Spindle number, density, and interelectrode coherence were reduced in the patient group and predicted overnight performance improvement. This impairment of sleep-dependent learning in schizophrenia is also present in daytime nap sleep (Seeck-Hirschner et al. 2010). Following a 40-min afternoon nap, visuomotor memory (mirror tracing) improved in healthy individuals and depressed patients. By contrast, medicated schizophrenia patients failed to improve and showed significantly reduced spindle density during their naps, although the correlation with performance was not significant. Manoach et al. (2010) compared the sleep and motor learning of medicated schizophrenia patients with demographically matched controls. They confirmed previous findings of spindle deficits in the patient group, reporting reductions in spindle power (13.5–15 Hz) and spindle density during the last quartile of sleep. Moreover, the patient group showed no overnight improvement on the motor task, in contrast to the control group which showed significant improvements that correlated with stage N2 duration.

Of note, spindles are also thought to block transmission of sensory information from lower brain structures to the cortex during sleep, resulting in decreased reactivity to stimuli, thereby promoting sleep continuity (Steriade et al. 1993). A failure of this gating mechanism would lead to a lower arousal threshold and more fragmented sleep. Therefore, in addition to impaired plasticity, spindle abnormalities may contribute to the common complaint of poor sleep quality and low sleep efficiency in schizophrenia.

7 The Thalamocortical Network in Sleep and Plasticity

Spindles and slow waves do not occur independently but rather participate in an important rhythmic network spanning cortical and subcortical structures. During sleep, almost all cortical neurons undergo a slow oscillation in membrane potential of <1 Hz (Steriade 2003). This underlying oscillation is a fundamental characteristic

of NREM sleep and temporally groups slow waves, spindles, and hippocampal ripples, supporting synchronized activity in distant brain regions. Coordinated activity across thalamocortical networks during NREM sleep plays a crucial role in brain plasticity. One key mechanism thought to underlie hippocampal-dependent memory is the reactivation of firing patterns in hippocampal and neocortical neurons. In this view of memory consolidation, a newly encoded memory trace is initially stored in the hippocampus, and then during sleep, the temporary trace is reactivated and transferred to the cortex where enduring plastic changes occur to form long-term memories. Animal and human studies suggest that this 'replaying' of memory traces is mediated by hippocampal ripples which are temporally correlated with sleep spindles, and that spindles, in turn, are typically phase-locked with slow waves. This temporal coordination may facilitate synaptic plasticity by aligning hippocampal replay activity with periods of high cortical excitability during the depolarized upstate of slow waves (Mölle and Born 2011).

The slow wave and spindle deficits observed in schizophrenia therefore point to a fundamental dysfunction of the thalamocortical network. This is corroborated by findings of disrupted functional and structural thalamocortical connectivity in MRI studies. Further support for this notion comes from a recent study in a rat model of schizophrenia. Administration of mitotoxin methylazoxymethanol acetate to pregnant rats results in offspring that exhibit physiological and cognitive dysfunction reminiscent of schizophrenia, including impaired spatial working memory. Phillips et al. (2012) reported that these animals also showed disruption of thalamocortical coordination during NREM sleep. Slow wave synchrony and propagation across the cortex were impaired, spindle phase-locking to delta waves was disrupted and hippocampal ripples were temporally uncoupled from spindles. This loss of coordination may underlie the cognitive and memory deficits seen in this rat model and in schizophrenia patients.

One possible cause of thalamocortical dyscoordination in schizophrenia is the thalamic reticular nucleus, a structural and functional hub of thalamocortical connectivity. In addition to its role as the spindle generator, the TRN is ideally placed to modulate bottom-up and top-down processes underlying higher cognitive function. It directly innervates the thalamus and receives excitatory inputs from thalamocortical and cortico-thalamic projections (Jones 2007). The TRN acts as an integrator of multiple functional modalities, amplifying relevant information and attenuating irrelevant or distracting information (Pinault 2011); as a result, the TRN has been central to theories of attention regulation (Crick 1984), sensory gating (Yingling and Skinner 1977), and self-representation (Vukadinovic 2011), all of which are impaired in schizophrenia. Evidence from molecular, animal, and human studies indicates a neurobiological dysfunction in the TRN in schizophrenia (for recent reviews, see Ferrarelli and Tononi 2011; Vukadinovic 2011).

TRN interneurons and outputs to thalamic relay nuclei are entirely GABAergic (Houser et al. 1980). The mechanism of synchronization across TRN cells is still largely unknown. GABAergic synapses between TRN neurons are one possibility; GABA receptors give rise to depolarizing currents in TRN neurons, which generate persistent spindle oscillations in these cells (Bazhenov et al. 1999; Golomb et al.

1994). Both dopamine and glutamate have been proposed to contribute to GABA hypofunction in the TRN, and the NMDAR-antagonist ketamine, which produces schizophrenia-like symptoms in humans and animals, has been shown to block thalamocortical rhythmicity (Buzsáki 1991). The GABA hypofunction observed in schizophrenia could therefore contribute to decreased spindle synchronicity, resulting in uncoordinated thalamocortical rhythms and consequently impaired plasticity.

The TRN also plays a role in embryonic development, providing axonal guidance for thalamocortical and cortical thalamic neurons (Pinault 2011). Animal studies indicate that aberrant TRN-dependent processes during critical periods of development could lead to higher-order cognitive impairments. Normally developing human and rat neonates exhibit spontaneous muscle twitches and jerks. In rats, sensory feedback from these movements triggers spindles in a somatotopic manner in primary somatosensory cortex (S1) and similar EEG bursts are observed in preterm infants (Khazipov et al. 2004); the authors hypothesize that coordinated motor-spindle activity establishes a map of the muscular system in S1 and strengthens developing thalamocortical and motor-sensory connections. Thus, spindle activity during fetal development may contribute to the development of neuronal self-representation. Importantly, an inability to correctly identify self-generated actions and thoughts may result in misattribution of mental experience to an external source and this can manifest itself as psychosis, including auditory hallucinations. Disruption of spindle-mediated plasticity during sensorimotor development could therefore contribute to positive symptoms of schizophrenia such as hearing voices (Vukadinovic 2011).

8 Impact of Medication on Sleep and Plasticity

There is a need for new drugs to treat schizophrenia, as many of the cognitive symptoms are not improved by medication (Reichenberg and Harvey 2007). The strong link between memory and spindles and slow waves makes them an attractive target for therapy. Most medications used to treat schizophrenia are thought to exert their antipsychotic effects through antagonism of dopamine receptors, but they may also interact with acetylcholine, serotonin, and histamine receptors. A drug's relative affinity for these different receptors gives rise to a variety of side effects, including sedation (via serotonergic and histaminergic pathways), movement abnormalities (via dopaminergic pathways), and disruption of REM sleep (via anticholinergic and serotonergic actions) (Krystal et al. 2008). Both spindles and slow waves are modulated by these neurotransmitter systems and are therefore sensitive to pharmacological manipulation by antipsychotics, with the potential for cognitive benefits as well as undesirable side effects.

Animal studies suggest that current antipsychotics interact with the TRN. Phencyclidine (PCP) is an NMDA-receptor antagonist that induces schizophrenia-like behavioral symptoms in humans and animals; therefore, it is used as a

pharmacological model of the disease. PCP administration in rats induced metabolic hypofunction within the TRN, which was reversed after coadministration of typical (haloperidol) or atypical (clozapine) antipsychotics with PCP (Cochran et al. 2002, 2003). PCP also induced excitotoxic lesions in the posterior cingulate and retrosplenial cortices of rats following injections into the anterior thalamus. These lesions were likely due to reduced inhibitory control of the TRN on anterior thalamic nuclei, which led to excessive activation (excitotoxicity) of corticolimbic areas. Importantly, these excitotoxic effects on the rat brain could be prevented by administering antipsychotic medications, such as haloperidol and clozapine (Olney et al. 1991; Sharp et al. 2001; Tomitaka et al. 2000). However, despite the interaction of current anti-psychotics with the TRN, they do not appear to normalize spindles in cross-sectional samples (Ferrarelli et al. 2010b). Within-subject trials are needed to confirm the effects of medication on spindle parameters.

Some recent studies have investigated the utility of drugs that influence spindle activity, with mixed success. A study in healthy individuals used zolpidem (Ambien) to increase the number of spindles during a daytime nap. The spindle increase was associated with improved verbal memory but not motor learning and was detrimental to perceptual learning (Mednick et al. 2013). Whether the decrement in perceptual learning related to increased spindles or some other effect of the drug is unclear. A recent study of medicated schizophrenic patients suggests a potential benefit of spindle enhancement, although the study may have been underpowered. Eszopiclone (Lunesta), a non-benzodiazepine hypnotic, was used to increase spindle number and density (Wamsley et al. 2013). The eszopiclone group showed significant overnight improvement on a motor learning task and the placebo group did not; however, the difference between the two groups was not significant. When the groups were combined, spindle number and density correlated with overnight motor task improvement, as has been shown in non-intervention studies.

Olanzapine and risperidone, although primarily antagonists of the D2 receptor, are thought to increase SWS through antagonism of serotonin-2 receptors (Krystal et al. 2008). Given the benefit of SWS to learning in healthy individuals, these agents might be expected to improve memory in schizophrenia. However, this hypothesis was not supported when olanzapine was administered to schizophrenia patients who were also chronically medicated with amisulpride, another atypical antipsychotic (Göder et al. 2008). Before bedtime, patients were trained on visuomotor and verbal memory tasks and then took a single dose of either olanzapine or placebo. SWS was increased in the olanzapine group as expected, but memory performance the following morning did not differ between groups. Spindle density was significantly decreased in the olanzapine group, which could have negated any putative benefits of increased SWS.

Manipulating sleeping brain activity to improve cognitive function in schizophrenia is a promising avenue of research, but it remains to be seen which sleep parameters should be targeted and which interventions are most effective. A better understanding of the cellular dynamics and neuropharmacology of sleep spindles and slow waves could provide new insights into the mechanisms of current drug actions and more focused targets for drug development.

9 Conclusion

Brain activity during sleep reveals important clues to the biological underpinnings of schizophrenia, a widespread mental illness with devastating consequences for individuals and society. Disrupted sleep appears to contribute to cognitive deficits including memory impairment and psychotic symptoms. Abnormalities of sleep EEG draw attention to dysfunction of plastic processes including neurodevelopment, neurotransmitter pathways, and specific neuronal structures such as the thalamic reticular nucleus and thalamocortical circuits. Further investigation of sleeping brain activity in schizophrenia has the potential to uncover mechanisms and biomarkers of the disease as well as provide promising targets for drug development.

References

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M (2002) Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci Official J Soc Neurosci 22(9), 3708–3719. doi:20026302

Abi-Dargham A, Xu X, Thompson JL, Gil R, Kegeles LS, Urban N, Hwang DR, Laruelle M, Slifstein M (2012) Increased prefrontal cortical D_1 receptors in drug naive patients with schizophrenia: a PET study with [^{11}C]NNC112. J Psychopharmacol 26(6):794–805. doi:10.1177/0269881111409265

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing, Arlington

Amzica F, Steriade M (1995) Disconnection of intracortical synaptic linkages disrupts synchronization of a slow oscillation. J Neurosci Official J Soc Neurosci 15(6):4658–4677

Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ (2004) Expression of disrupted-In-schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. Neuroscience 124(1):3–10. doi:10.1016/j.neuroscience.2003.11.010

Baddeley A (1992) Working memory. Science 255(5044):556–559

Barch DM, Moore H, Nee DE, Manoach DS, Luck SJ (2012) CNTRICS imaging biomarkers selection: Working memory. Schizophrenia Bull 38(1):43–52. doi:10.1093/schbul/sbr160

Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ (1999) Self-sustained rhythmic activity in the thalamic reticular nucleus mediated by depolarizing GABAA receptor potentials. Nature Neurosc 2(2):168–174. doi:10.1038/5729

Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992) Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatr 49(8):651–668; discussion 669–670

Bleuler E (1911) Dementia Praecox or the Group of Schizophrenias

Bodenmann S, Landolt H-P (2010) Effects of modafinil on the sleep EEG depend on Val158Met genotype of COMT. Sleep 33(8):1027–1035

Bodenmann S, Xu S, Luhmann UFO, Arand M, Berger W, Jung HH, Landolt H-P (2009) Pharmacogenetics of modafinil after sleep loss: catechol-O-methyltransferase genotype modulates waking functions but not recovery sleep. Clin Pharmacol Ther 85(3):296–304. doi:10.1038/clpt.2008.222

Borgwardt SJ, McGuire PK, Aston J, Gschwandtner U, Pflüger MO, Stieglitz RD, Radue EW, Riecher-Rössler A (2008) Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophr Res 106(2–3):108–114. doi:10.1016/j.schres.2008.08.007

Buchmann A, Ringli M, Kurth S, Schaerer M, Geiger A, Jenni OG, Huber R (2011) EEG sleep slow-wave activity as a mirror of cortical maturation. Cereb Cortex 21(3):607–615. doi:10.1093/cercor/bhq129

Buzsáki G (1991) The thalamic clock: emergent network properties. Neuroscience 41(2–3):351–364

Carter CS, Minzenberg M, West R, Macdonald A 3rd (2012) CNTRICS imaging biomarker selections: executive control paradigms. Schizophr Bull 38(1):34–42. doi:10.1093/schbul/sbr114

Centonze D, Usiello A, Costa C, Picconi B, Erbs E, Bernardi G, Calabresi P (2004) Chronic haloperidol promotes corticostriatal long-term potentiation by targeting dopamine D2L receptors. J Neurosci Official J Soc Neurosci 24(38):8214–8222. doi:10.1523/JNEUROSCI.1274-04.2004

Chouinard S, Poulin J, Stip E, Godbout R (2004) Sleep in untreated patients with schizophrenia: a meta-analysis. Schizophr Bull 30(4):957–967

Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK (2008) The DISC locus in psychiatric illness. Mol Psychiatry 13(1):36–64. doi:10.1038/sj.mp.4002106

Chugani HT, Phelps ME, Mazziotta JC (1987) Positron emission tomography study of human brain functional development. Ann Neurol 22(4):487–497. doi:10.1002/ana.410220408

Cirillo MA, Seidman LJ (2003) Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. Neuropsychol Rev 13(2):43–77

Clare L, McKenna PJ, Mortimer AM, Baddeley AD (1993) Memory in schizophrenia: what is impaired and what is preserved? Neuropsychologia 31(11):1225–1241. doi:10.1016/0028-3932(93)90070-G

Cochran SM, Fujimura M, Morris BJ, Pratt JA (2002) Acute and delayed effects of phencyclidine upon mRNA levels of markers of glutamatergic and GABAergic neurotransmitter function in the rat brain. Synapse 46(3):206–214. doi:10.1002/syn.10126

Cochran SM, Kennedy M, McKerchar CE, Steward LJ, Pratt JA, Morris BJ (2003) Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: differential modulation by antipsychotic drugs. Neuropsychopharmacology. Official Publ Am Coll Neuropsychopharmacol 28(2):265–275. doi:10.1038/sj.npp.1300031

Crick F (1984) Function of the thalamic reticular complex: the searchlight hypothesis. Proc Nat Acad Sci USA 81(14):4586–4590

Crook JM, Tomaskovic-Crook E, Copolov DL, Dean B (2000) Decreased muscarinic receptor binding in subjects with schizophrenia: a study of the human hippocampal formation. Biol Psychiatry 48(5):381–388. doi:10.1016/S0006-3223(00)00918-5

Crook JM, Tomaskovic-Crook E, Copolov DL, Dean B (2001) Low muscarinic receptor binding in prefrontal cortex from subjects with schizophrenia: a study of Brodmann's areas 8, 9, 10, and 46 and the effects of neuroleptic drug treatment. Am J Psychiatry 158(6):918–925

Cross-Disorder Group of the Psychiatric Genomics Consortium, Smoller JW, Craddock N, Kendler K, Lee PH, Neale BM, Sullivan PF, et al (2013) Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381(9875):1371–1379. doi:10.1016/S0140-6736(12)62129-1

Dement W (1955) Dream recall and eye movements during sleep in schizophrenics and normals. J Nerv Ment Dis 122(3):263–269

Doyon J, Orban P, Barakat M, Debas K, Lungu O, Albouy G, Benali H et al (2011) Plasticité du Cerveau Associée à l'Apprentissage Moteur. Méd Sci M/S 27(4):413–420. doi:10.1051/medsci/2011274018

Drever BD, Riedel G, Platt B (2011) The cholinergic system and hippocampal plasticity. Behav Brain Res 221(2):505–514. doi:10.1016/j.bbr.2010.11.037

Drummond SPA, Anderson DE, Straus LD, Vogel EK, Perez VB (2012) The effects of two types of sleep deprivation on visual working memory capacity and filtering efficiency. PLoS ONE 7(4). doi:10.1371/journal.pone.0035653

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000) Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project. Am J Psychiatry 157 (9):1416–1422

Esser SK, Hill SL, Tononi G (2007) Sleep homeostasis and cortical synchronization: i. modeling the effects of synaptic strength on sleep slow waves. Sleep 30(12):1617–1630

Fatemi SH, Folsom TD (2009) The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull 35(3):528–548. doi:10.1093/schbul/sbn187

Feinberg I, Campbell IG (2010) Sleep EEG changes during adolescence: an index of a fundamental brain reorganization. Brain Cogn 72(1):56–65. doi:10.1016/j.bandc.2009.09.008

Feinberg I, Braun M, Koresko RL, Gottlieb F (1969) Stage 4 sleep in schizophrenia. Arch Gen Psychiatry 21(3):262–266

Ferrarelli F (2013) Endophenotypes and biological markers and of schizophrenia: from biological signs of illness to novel treatment targets. Curr Pharm Des

Ferrarelli F, Tononi G (2011) The thalamic reticular nucleus and schizophrenia. Schizophrenia Bull 37(2):306–315. doi:10.1093/schbul/sbq142

Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, Watson A, Bria P, Tononi G (2007) Reduced sleep spindle activity in schizophrenia patients. Am J Psychiatry 164 (3):483–492. doi:10.1176/appi.ajp.164.3.483

Ferrarelli F, Peterson MJ, Sarasso S, Riedner BA, Murphy MJ, Benca RM, Bria P, Kalin NH, Tononi G (2010a) Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. Am J Psychiatry 167(11):1339–1348. doi:10.1176/appi.ajp.2010.09121731

Ferrarelli F, Peterson MJ, Sarasso S, Riedner BA, Murphy MJ, Benca RM, Bria P, Kalin NH, Tononi G (2010b) Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. Am J Psychiatry 167(11):1339–1348. doi:10.1176/appi.ajp.2010.09121731

Fisher SP, Vyazovskiy VV (2014) Local sleep taking care of high-maintenance cortical circuits under sleep restriction. Sleep 37(11):1727–1730. doi:10.5665/sleep.4156

Florán B, Florán L, Erlij D, Aceves J (2004) Activation of dopamine D4 receptors modulates [3H] GABA release in slices of the rat thalamic reticular nucleus. Neuropharmacology 46(4):497–503. doi:10.1016/j.neuropharm.2003.10.004

Fogel SM, Smith CT (2011) The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35(5):1154–1165. doi:10.1016/j.neubiorev.2010.12.003

Forest G, Poulin J, Daoust A-M, Lussier I, Stip E, Godbout R (2007) Attention and non-REM sleep in neuroleptic-naive persons with schizophrenia and control participants. Psychiatry Res 149:33–40. doi:10.1016/j.psychres.2005.11.005

Fusar-Poli P, Meyer-Lindenberg A (2013) Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. Schizophr Bull 39(1):33–42. doi:10.1093/schbul/sbr180

Gais S, Born J (2004) Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc Nat Acad Sci USA 101(7):2140–2144

Gandia JA, De Las Heras S, García M, Giménez-Amaya JM (1993) Afferent projections to the reticular thalamic nucleus from the globus pallidus and the substantia nigra in the rat. Brain Res Bull 32(4):351–358

Gao WJ, Krimer LS, Goldman-Rakic PS (2001) Presynaptic regulation of recurrent excitation by D1 receptors in prefrontal circuits. Proc Natl Acad Sci USA 98:295–300. doi:10.1073/pnas.011524298

García-Cabezas MA, Rico B, Sánchez-González MA, Cavada C (2007) Distribution of the dopamine innervation in the macaque and human thalamus. NeuroImage 34(3):965–984. doi:10.1016/j.neuroimage.2006.07.032

Gaser C, Nenadic I, Buchsbaum BR, Hazlett EA, Buchsbaum MS (2004) Ventricular enlargement in schizophrenia related to volume reduction of the thalamus, striatum, and superior temporal cortex. Am J Psychiatry 161(1):154–156

Gilmour G, Dix S, Fellini L, Gastambide F, Plath N, Steckler T, Talpos J, Tricklebank M (2012) NMDA receptors, cognition and schizophrenia—testing the validity of the NMDA receptor hypofunction hypothesis. Neuropharmacology 62(3):1401–1412. doi:10.1016/j.neuropharm.2011.03.015

Göder R, Boigs M, Braun S, Friege L, Fritzer G, Aldenhoff JB, Hinze-Selch D (2004) Impairment of visuospatial memory is associated with decreased slow wave sleep in schizophrenia. J Psychiatric Res 38(6):591–599. doi:10.1016/j.jpsychires.2004.04.005

Göder R, Fritzer G, Gottwald B, Lippmann B, Seeck-Hirschner M, Serafin I, Aldenhoff JB (2008) Effects of olanzapine on slow wave sleep, sleep spindles and sleep-related memory consolidation in schizophrenia. Pharmacopsychiatry 41(3):92–99. doi:10.1055/s-2007-1004592

Göder R, Baier PC, Beith B, Baecker C, Seeck-Hirschner M, Junghanns K, Marshall L (2013) Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. Schizophr Res 144(1–3):153–154. doi:10.1016/j.schres.2012.12.014

Goel N, Abe T, Braun ME, Dinges DF (2014) Cognitive workload and sleep restriction interact to influence sleep homeostatic responses. Sleep 37(11):1745–1756. doi:10.5665/sleep.4164

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Thompson PM et al (2004) Dynamic mapping of human cortical development during childhood through early adulthood. Proc Nat Acad Sci USA 101(21):8174–8179. doi:10.1073/pnas.0402680101

Golomb D, Wang XJ, Rinzel J (1994) Synchronization properties of spindle oscillations in a thalamic reticular nucleus model. J Neurophysiol 72(3):1109–1126

González S, Moreno-Delgado D, Moreno E, Pérez-Capote K, Franco R, Mallol J, McCormick PJ et al (2012) Circadian-related heteromerization of adrenergic and dopamine D4 receptors modulates melatonin synthesis and release in the pineal gland. PLoS Biol 10(6):e1001347. doi:10.1371/journal.pbio.1001347

Govindaiah G, Wang T, Gillette MU, Crandall SR, Cox CL (2010) Regulation of inhibitory synapses by presynaptic D4 dopamine receptors in thalamus. J Neurophysiol 104(5):2757–2765. doi:10.1152/jn.00361.2010

Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS (2007) The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. Schizophr Bull 33(1):49–68. doi:10.1093/schbul/sbl055

Hagewoud R, Havekes R, Novati A, Keijser JN, Van der Zee EA, Meerlo P (2010) Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. J Sleep Res 19(2):280–288. doi:10.1111/j.1365-2869.2009.00799.x

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS Biol 6(7):e159. doi:10.1371/journal.pbio.0060159

Hasenkamp W, James GA, Boshoven W, Duncan E (2011) Altered engagement of attention and default networks during target detection in schizophrenia. Schizophr Res 125(2–3):169–173. doi:10.1016/j.schres.2010.08.041

Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12(3):426–445

Hiatt JF, Floyd TC, Katz PH, Feinberg I (1985) Further evidence of abnormal non-rapid-eye-movement sleep in schizophrenia. Arch Gen Psychiatry 42(8):797–802

Horan WP, Braff DL, Nuechterlein KH, Sugar CA, Cadenhead KS, Calkins ME, Green MF et al (2008) Verbal working memory impairments in individuals with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia. Schizophr Res 103(1–3):218–228. doi:10.1016/j.schres.2008.02.014

Houser CR, Vaughn JE, Barber RP, Roberts E (1980) GABA neurons are the major cell type of the nucleus reticularis thalami. Brain Res 200(2):341–354

Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophr Bull 35(3):549–562. doi:10.1093/schbul/sbp006

Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S (2012) The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry 69(8):776–786. doi:10.1001/archgenpsychiatry.2012.169

Huber R, Felice Ghilardi M, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430 (6995):78–81. doi:10.1038/nature02663

Huttenlocher PR, Dabholkar AS (1997) Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 387(2):167–178

Jones BE (2005) From waking to sleeping: neuronal and chemical substrates. Trends Pharmacol Sci 26(11):578–586. doi:10.1016/j.tips.2005.09.009

Jones E (ed) (2007) The thalamus, 2nd edn. Cambridge University Press, Cambridge

Kawada R, Yoshizumi M, Hirao K, Fujiwara H, Miyata J, Shimizu M, Namiki C, Sawamoto N, Fukuyama H, Hayashi T, Murai T (2009) Brain volume and dysexecutive behavior in schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 33(7):1255–1260. doi:10.1016/j.pnpbp.2009.07.014

Kempenaers C, Kerkhofs M, Linkowski P, Mendlewicz J (1988) Sleep EEG variables in young schizophrenic and depressive patients. Biol Psychiatry 24(7):833–838

Keshavan MS, Reynolds CF 3rd, Miewald MJ, Montrose DM, Sweeney JA, Vasko RC Jr, Kupfer DJ (1998) Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. Archiv Gen Psychiatry 55(5):443–448

Keshavan MS, Diwadkar VA, Montrose DM, Stanley JA, Pettegrew JW (2004) Premorbid characterization in schizophrenia: the Pittsburgh high risk study. World Psychiatry 3 (3):163–168

Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsáki G (2004) Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature 432(7018):758–761. doi:10.1038/nature03132

Kim Y, Zerwas S, Trace SE, Sullivan PF (2011) Schizophrenia genetics: where next? Schizophr Bull 37(3):456–463. doi:10.1093/schbul/sbr031

Kirkwood A, Rozas C, Kirkwood J, Perez F, Bear MF (1999) Modulation of long-term synaptic depression in visual cortex by acetylcholine and norepinephrine. J Neurosci Official J Soc Neurosci 19(5):1599–1609

Kopp C, Longordo F, Nicholson JR, Lüthi A (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. J Neurosci Official J Soc Neurosci 26(48):12456–12465. doi:10.1523/JNEUROSCI.2702-06.2006

Krystal AD, Goforth HW, Roth T (2008) Effects of antipsychotic medications on sleep in schizophrenia. Int Clin Psychopharmacol 23(3):150–160. doi:10.1097/YIC.0b013e3282f39703

Kupfer DJ, Wyatt RJ, Scott J, Snyder F (1970) Sleep disturbance in acute schizophrenic patients. Am J Psychiatry 126(9):1213–1223

Kuriyama K, Mishima K, Suzuki H, Aritake S, Uchiyama M (2008) Sleep accelerates the improvement in working memory performance. J Neurosci 28(40):10145–10150. doi:10.1523/JNEUROSCI.2039-08.2008

Kyriakopoulos M, Frangou S (2009) Recent diffusion tensor imaging findings in early stages of schizophrenia. Curr Opin Psychiatry 22(2):168–176. doi:10.1097/YCO.0b013e328325aa23

Landsness EC, Ferrarelli F, Sarasso S, Goldstein MR, Riedner BA, Cirelli C, Perfetti B, Moisello C, Ghilardi MF, Tononi G (2011) Electrophysiological traces of visuomotor learning and their renormalization after sleep. Clin Neurophysiol 122:2418–2425. doi:10.1016/j.clinph.2011.05.001

Lauer CJ, Schreiber W, Pollmächer T, Holsboer F, Krieg JC (1997) Sleep in schizophrenia: a polysomnographic study on drug-naive patients. Neuropsychopharmacology. Official Publ Am Coll Neuropsychopharmacol 16(1):51–60. doi:10.1016/S0893-133X(96)00159-5

Laursen TM, Munk-Olsen T, Vestergaard M (2012) Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr Opin Psychiatry 25(2):83–88. doi:10.1097/YCO.0b013e32835035ca

Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C (2012) Diffusion tensor imaging of white matter tract evolution over the lifespan. NeuroImage 60(1):340–352. doi:10.1016/j.neuroimage.2011.11.094

Lee SH, DeCandia TR, Ripke S, Yang J, Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ), International Schizophrenia Consortium (ISC), Wray NR, et al (2012) Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nature Genet 44(3):247–250. doi:10.1038/ng.1108

MacDonald AW, Schulz SC (2009) What we know: findings that every theory of schizophrenia should explain. Schizophr Bull 35(3):493–508. doi:10.1093/schbul/sbp017

Manoach DS, Stickgold R (2009) Does abnormal sleep impair memory consolidation in schizophrenia? Front Hum Neurosci 3:21. doi:10.3389/neuro.09.021.2009

Manoach DS, Cain MS, Vangel MG, Khurana A, Goff DC, Stickgold R (2004) A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. Biol Psychiatry 56 (12):951–956. doi:10.1016/j.biopsych.2004.09.012

Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E, Djonlagic I, Vangel MG, Goff DC, Stickgold R (2010) Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. J Psychiatr Res 44(2):112–120. doi:10.1016/j.jpsychires.2009.06.011

Maret S, Faraguna U, Nelson AB, Cirelli C, Tononi G (2011) Sleep and waking modulate spine turnover in the adolescent mouse cortex. Nature Neurosci 14(11):1418–1420. doi:10.1038/nn.2934

Marks GA, Birabil CG (1998) Enhancement of rapid eye movement sleep in the rat by cholinergic and adenosinergic agonists infused into the pontine reticular formation. Neuroscience 86 (1):29–37

Marsman A, Heuvel MP van den, Klomp DWJ, Kahn RS, Luijten PR, Pol HEH (2013) Glutamate in Schizophrenia: A Focused Review and Meta-Analysis of 1H-MRS Studies. Schizophr Bull 39:120–129. doi:10.1093/schbul/sbr069

Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G (2004) The sleep slow oscillation as a traveling wave. J Neurosci 24(31):6862–6870. doi:10.1523/JNEUROSCI.1318-04.2004

McIntosh AM, Muñoz Maniega S, Lymer GKS, McKirdy J, Hall J, Sussmann JED, Bastin ME, Clayden JD, Lawrie SM (2008) White matter tractography in bipolar disorder and schizophrenia. Biol Psychiatry 64(12):1088–1092. doi:10.1016/j.biopsych.2008.07.026

Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, Drummond SPA (2013) The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. J Neurosci Official J Soc Neurosci 33(10):4494–4504. doi:10.1523/JNEUROSCI.3127-12.2013

Mölle M, Born J (2011) Slow oscillations orchestrating fast oscillations and memory consolidation. Prog Brain Res 193:93–110. doi:10.1016/B978-0-444-53839-0.00007-7

Monti JM, Jantos H (2008) The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. In: Esposito E, Di Matteo V, Di Giovanni G (eds) Progress in brain research, vol 172, pp 625–646. Elsevier, New York. Retrieved from http://www.sciencedirect.com/science/article/pii/S0079612308009291

Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, Goldman-Rakic PS (1996) Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. Nature 381(6579):245–248. doi:10.1038/381245a0

Murphy M, Riedner BA, Huber R, Massimini M, Ferrarelli F, Tononi G (2009) Source modeling sleep slow waves. Proc Nat Acad Sci USA 106(5):1608–1613. doi:10.1073/pnas.0807933106

Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, Tononi G (2011) Regional slow waves and spindles in human sleep. Neuron 70(1):153–169. doi:10.1016/j.neuron.2011.02.043

Nuechterlein KH (1983) Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. J Abnorm Psychology 92 (1):4–28

Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA (1991) NMDA antagonist neurotoxicity: mechanism and prevention. Science 254(5037):1515–1518

Olney JW, Newcomer JW, Farber NB (1999) NMDA receptor hypofunction model of schizophrenia. J Psychiatric Res 33(6):523–533. doi:10.1016/S0022-3956(99)00029-1

Owen MJ (2012) Implications of genetic findings for understanding schizophrenia. Schizophre Bull 38(5):904–907. doi:10.1093/schbul/sbs103

Petanjek Z, Judas M, Kostović I, Uylings HBM (2008) Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: a layer-specific pattern. Cereb Cortex 18 (4):915–929. doi:10.1093/cercor/bhm124

Phillips KG, Bartsch U, McCarthy AP, Edgar DM, Tricklebank MD, Wafford KA, Jones MW (2012) Decoupling of sleep-dependent cortical and hippocampal interactions in a neurodevelopmental model of schizophrenia. Neuron 76(3):526–533. doi:10.1016/j.neuron.2012.09.016

Picciotto MR, Higley MJ, Mineur YS (2012) Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron 76:116–129. doi:10.1016/j.neuron.2012.08.036

Pinault D (2011) Dysfunctional thalamus-related networks in schizophrenia. Schizophr Bull 37 (2):238–243. doi:10.1093/schbul/sbq165

Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9:534–547. doi:10.1162/jocn.1997.9.4.534

Poulin J, Daoust A-M, Forest G, Stip E, Godbout R (2003) Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. Schizophre Res 62 (1–2):147–153

Raedler TJ, Knable MB, Jones DW, Urbina RA, Gorey JG, Lee KS, Egan MF, Coppola R, Weinberger DR (2003) In vivo determination of muscarinic acetylcholine receptor availability in schizophrenia. Am J Psychiatry 160(1):118–127

Ragland JD, Cohen NJ, Cools R, Frank MJ, Hannula DE, Ranganath C (2012) CNTRICS imaging biomarkers final task selection: long-term memory and reinforcement learning. Schizophr Bull 38(1):62–72. doi:10.1093/schbul/sbr168

Rapoport JL, Giedd JN, Gogtay N (2012) Neurodevelopmental model of schizophrenia: update 2012. Mol Psychiatry 17(12):1228–1238. doi:10.1038/mp.2012.23

Rasch B, Gais S, Born J (2009) Impaired off-line consolidation of motor memories after combined blockade of cholinergic receptors during REM sleep-rich sleep. Neuropsychopharmacology 34 (7):1843–1853. doi:10.1038/npp.2009.6

Rechtschaffen A, Schulsinger F, Mednick SA (1964) Schizophrenia and physiological indices of dreaming. Arch Gen Psychiatry 10:89–93

Reichenberg A, Harvey PD (2007) Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. Psychol Bull 133(5):833–858. doi:10.1037/0033-2909.133.5.833

Ren W, Lui S, Deng W, Li F, Li M, Huang X, Wang Y, Li T, Sweeney JA, Gong Q (2013). Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. Am J Psychiatry. doi:10.1176/appi.ajp.2013.12091148

Riemann D, Hohagen F, Bahro M, Lis S, Stadmüller G, Gann H, Berger M (1994) Cholinergic neurotransmission, REM sleep and depression. J Psychosom Res 38(Suppl 1):15–25

Sarter M, Lustig C, Taylor SF (2012) Cholinergic contributions to the cognitive symptoms of schizophrenia and the viability of cholinergic treatments. Neuropharmacology 62(3):1544–1553. doi:10.1016/j.neuropharm.2010.12.001

Sawamura N, Ando T, Maruyama Y, Fujimuro M, Mochizuki H, Honjo K, Sawa A et al (2008) Nuclear DISC1 regulates CRE-mediated gene transcription and sleep homeostasis in the fruit fly. Molecular Psychiatry 13(12):1138–1148. doi:10.1038/mp.2008.101

Schabus M, Dang-Vu TT, Albouy G, Balteau E, Boly M, Carrier J, Maquet P et al (2007) Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Nat Acad Sci USA 104(32):13164–13169. doi:10.1073/pnas.0703084104

Seeck-Hirschner M, Baier PC, Sever S, Buschbacher A, Aldenhoff JB, Göder R (2010) Effects of daytime naps on procedural and declarative memory in patients with schizophrenia. J Psychiatr Res 44(1):42–47. doi:10.1016/j.jpsychires.2009.05.008

Seeman P, Guan HC, Van Tol HH (1993) Dopamine D4 receptors elevated in schizophrenia. Nature 365(6445):441–445. doi:10.1038/365441a0

Sekimoto M, Kato M, Watanabe T, Kajimura N, Takahashi K (2007) Reduced frontal asymmetry of delta waves during all-night sleep in schizophrenia. Schizophr Bull 33(6):1307–1311. doi:10.1093/schbul/sbl069

Sekimoto M, Kato M, Watanabe T, Kajimura N, Takahashi K (2011) Cortical regional differences of delta waves during all-night sleep in schizophrenia. Schizophr Res 126(1–3):284–290. doi:10.1016/j.schres.2010.11.003

Sharp FR, Tomitaka M, Bernaudin M, Tomitaka S (2001) Psychosis: pathological activation of limbic thalamocortical circuits by psychomimetics and schizophrenia? Trends Neurosci 24 (6):330–334

Siegel JM (2011) REM sleep. In: Principles and practice of sleep medicine 5th edn. W.B. Saunders, Philadelphia, pp 92–111. Retrieved from http://www.sciencedirect.com/science/article/pii/B9781416066453000086

Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, Kahn RS (2004) Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res 71(2–3):285–295. doi:10.1016/j.schres.2004.03.007

Skudlarski P, Jagannathan K, Anderson K, Stevens MC, Calhoun VD, Skudlarska BA, Pearlson G (2010) Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. Biol Psychiatry 68(1):61–69. doi:10.1016/j.biopsych.2010.03.035

Snitz BE, Macdonald AW 3rd, Carter CS (2006) Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull 32(1):179–194. doi:10.1093/schbul/sbi048

Stephan KE, Baldeweg T, Friston KJ (2006) Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry 59(10):929–939. doi:10.1016/j.biopsych.2005.10.005

Stephan KE, Friston KJ, Frith CD (2009) Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 35(3):509–527. doi:10.1093/schbul/sbn176

Steriade M (2003) The corticothalamic system in sleep. Front Biosci J Virtual Libr 8:d878–d899

Steriade M, McCormick DA, Sejnowski TJ (1993) Thalamocortical oscillations in the sleeping and aroused brain. Science 262(5134):679–685. doi:10.1126/science.8235588

Stickgold R, James L, Hobson JA (2000) Visual discrimination learning requires sleep after training. Nat Neurosci 3:1237–1238. doi:10.1038/81756

Sullivan PF, Kendler KS, Neale MC (2003) Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Archiv Gen Psychiatry 60(12):1187–1192. doi:10.1001/archpsyc.60.12.1187

Tandon R, Shipley JE, Taylor S, Greden JF, Eiser A, DeQuardo J, Goodson J (1992) Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. Arch Gen Psychiatry 49(3):185–194

Tarokh L, Carskadon MA (2010) Developmental changes in the human sleep EEG during early adolescence. Sleep 33(6):801–809

Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Rapoport JL et al (2001) Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Nat Acad Sci 98(20):11650–11655. doi:10.1073/pnas.201243998

Timofeev I, Grenier F, Bazhenov M, Sejnowski TJ, Steriade M (2000) Origin of slow cortical oscillations in deafferented cortical slabs. Cerebr Cortex 10(12):1185–1199

Tomitaka S, Tomitaka M, Tolliver BK, Sharp FR (2000) Bilateral blockade of NMDA receptors in anterior thalamus by dizocilpine (MK-801) injures pyramidal neurons in rat retrosplenial cortex. Eur J Neurosci 12(4):1420–1430

Traub AC (1972) Sleep stage deficits in chronic schizophrenia. Psychol Rep 31(3):815–820

Tritsch NX, Sabatini BL (2012) Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron 76(1):33–50. doi:10.1016/j.neuron.2012.09.023

Tseng KY, O'Donnell P (2004) Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. J Neurosci Official J Soc Neurosci 24(22):5131–5139. doi:10.1523/JNEUROSCI.1021-04.2004

Van Cauter E, Linkowski P, Kerkhofs M, Hubain P, L'Hermite-Balériaux M, Leclercq R, Mendlewicz J et al (1991) Circadian and sleep-related endocrine rhythms in schizophrenia. Archives of General Psychiatry 48(4):348–356

Vukadinovic Z (2011) Sleep abnormalities in schizophrenia may suggest impaired trans-thalamic cortico-cortical communication: towards a dynamic model of the illness. Eur J Neurosci 34 (7):1031–1039. doi:10.1111/j.1460-9568.2011.07822.x

Vyazovskiy VV, Olcese U, Lazimy YM, Faraguna U, Esser SK, Williams JC, Tononi G et al (2009) Cortical firing and sleep homeostasis. Neuron 63(6):865–878. doi:10.1016/j.neuron.2009.08.024

Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, Manoach DS et al (2012) Reduced Sleep Spindles and Spindle Coherence in Schizophrenia: Mechanisms of Impaired Memory Consolidation? Biological Psychiatry 71(2):154–161. doi:10.1016/j.biopsych.2011.08.008

Wamsley EJ, Shinn AK, Tucker MA, Ono KE, McKinley SK, Ely AV, Manoach DS et al (2013) The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: a randomized placebo-controlled trial. Sleep 36(9):1369–1376. doi:10.5665/sleep.2968

Weickert TW (2002) Habit and skill learning in schizophrenia: evidence of normal striatal processing with abnormal cortical input. Learn Mem 9(6):430–442. doi:10.1101/lm.49102

Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, Goldberg TE et al (2001) Prefrontal neurons and the genetics of schizophrenia. Biological Psychiatry 50 (11):825–844

Yingling C, Skinner J (1977) Gating of thalamic input to cerebral cortex by nucleus reticularis thalami. In: Desmedt J (ed) Attention, voluntary contraction and event-related cerebral potentials, vol 1. Karger, Basel, pp 70–96

Yun SH, Cheong MY, Mook-Jung I, Huh K, Lee C, Jung MW (2000) Cholinergic modulation of synaptic transmission and plasticity in entorhinal cortex and hippocampus of the rat. Neuroscience 97(4):671–676

Zarcone VP Jr, Benson KL, Berger PA (1987) Abnormal rapid eye movement latencies in schizophrenia. Arch Gen Psychiatry 44(1):45–48

Chronically Restricted or Disrupted Sleep as a Causal Factor in the Development of Depression

Peter Meerlo, Robbert Havekes and Axel Steiger

Abstract Sleep problems are a common complaint in the majority of people suffering from depression. While sleep complaints were traditionally seen as a symptom of mood disorders, accumulating evidence suggests that in many cases the relationship may be reverse as well. A long list of longitudinal studies shows that sleep complaints often precede the onset of depression and constitute an independent risk factor for the development of the disorder. Additionally, experimental studies in animals show that chronically restricted or disrupted sleep may gradually induce neurobiological changes that are very similar to what has been reported for depressed patients. The mechanisms through which insufficient sleep increases the risk for depression are poorly understood but may include effects of sleep disturbance on neuroendocrine stress systems, serotonergic neurotransmission, and various interacting signaling pathways involved in the regulation of neuronal plasticity and neurogenesis. Because sleep is considered to play a crucial role in regulating neuronal plasticity and synaptic strength, chronically insufficient sleep may contribute to depression through an impairment of these plasticity processes leading to altered connectivity and communication within and between brain regions involved in the regulation of mood.

Keywords Sleep deprivation · Sleep disturbance · Insomnia · Mood disorders · Depression · Neuronal plasticity · Neurotrophic factors · Neurogenesis · Serotonin · Glucocorticoids · Stress

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Contents

1 Introduction

Frequently restricted or disrupted sleep is a widespread and serious problem in our Western society (Bonnet and Arand 1995; Rajaratnam and Arendt 2001). Many people experience insufficient sleep on a regular basis due to our modern around-the-clock lifestyle, high work pressure, and psychosocial stress. Because sleep is generally thought to be a process that serves a crucial role in neuronal recovery, maintenance, and plasticity, insufficient sleep may have important repercussions for brain function. Whereas subjects may initially recover from the adverse effects of short or disrupted sleep with a subsequent period of recovery sleep, frequent or chronic sleep loss may induce neurobiological changes that are not immediately evident but accumulate over time, ultimately with serious health consequences (Banks and Dinges 2007; Meerlo et al. 2008). Indeed, sleep complaints and restricted sleep have been identified as risk factors for various diseases including psychiatric disorders (Baglioni et al. 2011; Benca and Peterson 2008; Riemann and Voderholzer 2003). Especially in the case of depression, the association with sleep complaints is particularly strong. While sleep disturbance was traditionally seen as a symptom of mood disorders, numerous studies now clearly suggest that the relationship between sleep changes and depression is more complex and may work in the other direction as well. Instead of being a symptom, insufficient sleep may act as a causal factor that sensitizes individuals, contributes to the development of depression, exacerbates the symptoms, and reduces the efficacy of pharmacological treatment (Baglioni et al. 2011; Benca and Peterson 2008; Riemann and Voderholzer 2003). In this overview, we will summarize different lines of research supporting the idea that insufficient sleep may contribute to depression and also discuss the potential molecular and neurobiological mechanisms underlying this relationship.

2 Insufficient Sleep as a Risk Factor for Developing Depression

Ford and Kamerow in (1989) published one of the first longitudinal, prospective studies establishing sleep complaints as a predictor of psychiatric disorders, including depression. Close to 8,000 adult individuals were questioned about their sleep and psychiatric symptoms at baseline and 1 year later. The prevalence of psychiatric symptoms in general and depression in particular was much higher in those subjects suffering from insomnia as compared to those without sleep complaints. Importantly, among the individuals that reported insomnia at both interviews, there were significantly more new, first-time cases of major depression at the second interview, indicating that in these cases insomnia preceded the onset of depression.

In another longitudinal, prospective study, a random sample of 21–30 years old adults were interviewed 3 years apart (Breslau et al. 1996). The relative risk for new onset of major depression during this period was nearly 4 times higher in subjects with a history of insomnia as compared to those without insomnia. Even when a history of other symptoms that also predict depression was controlled for, such as concentration problems and suicidal ideation, there was still a twofold increased risk for new major depression in subjects with a history of insomnia. Although such other symptoms may be confounders in the association between sleep disturbance and subsequent depression, one has to keep in mind that they may actually be mediators as well. The effect of sleep loss on the ability to concentrate is obvious, but there are many studies that suggest sleep disturbance may be causal to, e.g., suicidal thoughts as well (Liu and Buysse 2005).

The Johns Hopkins Precursors study was another important prospective study on the relationship between self-reported sleep disturbances and subsequent depression, one with a follow-up period that spanned 1–45 years (Chang et al. 1997). Over 1,000 young, male students provided information on their sleep habits during medical school and were then followed after graduation through midlife. Over 100 individuals at one point or another developed clinical depression, 13 of which committed suicide. The relative risk of clinical depression was 2 times higher in those who had reported insomnia in medical school compared to those without sleep complaints. The risk of developing depression was also 1.8 times higher in those men with difficulties sleeping under stress in medical school as compared to those who did not report these difficulties. These findings suggest that poor sleep may be an indicator of increased risk for depression already at a very early stage.

Many other studies have by now confirmed that sleep complaints often precede and predict the onset of depression (e.g., Buysse et al. 2008; Gregory et al. 2005; Mallon et al. 2000). A recent meta-analysis of 21 relevant studies estimated that, on average, non-depressed people with insomnia have a more than twofold higher risk to develop depression than people without sleep complaints (Baglioni et al. 2011).

Importantly, restricted or disrupted sleep in our society is a problem that not only affects adults but is increasingly common among young children and adolescents as well (Meijer et al. 2000; Van den Bulck 2004), and several studies have established

a clear longitudinal relationship with early life depression (e.g., Buysse et al. 2008; Gregory et al. 2009; Liu et al. 2007; Roane and Taylor 2008; Roberts and Duong 2013). For instance, sleep problems already at an age of 8 significantly predicted the occurrence of depressive symptoms at age 10 (Gregory et al. 2009). Also, adolescents with bedtimes of midnight or later were 24 % more likely to suffer from depression and 20 % more likely to have suicidal ideation than adolescents with parental-set bedtimes of 10 PM or earlier (Gangwisch et al. 2010). Because later bedtimes were associated with shorter sleep duration, these data in young people support the view that short and insufficient sleep may play a role in the development of depression.

Several other studies have also reported that short or disturbed sleep is a significant predictor of suicidal ideation and behavior, both in children (Fitzgerald et al. 2011; Lee et al. 2012; Liu and Buysse 2005) and adults (Agargun et al. 1997; Bernert et al. 2005; Goodwin and Marusic 2008). Although in many cases this effect of sleep disturbance may be mediated by depression, a recent meta-analysis showed that the association between sleep disturbance and suicidal behavior persists even when controlled for depression (Pigeon et al. 2012).

While the findings discussed so far clearly suggest that chronically restricted or disrupted sleep constitutes an independent risk factor for the development of depression, other studies suggest that disrupted sleep may also maintain depression and hamper the efficacy of treatment (e.g., Emslie et al. 2012; Hatzinger et al. 2004; Pigeon et al. 2008). For instance, the results from a large multisite randomized trial showed that depressive patients with persistent sleep complaints responded less well to antidepressant treatment and were 1.8–3.5 times more likely to remain depressed than patients without sleep complaints (Pigeon et al. 2008). Such findings strongly support the notion that sleep problems need to be considered as a crucial symptom that should be an important focus of antidepressant treatment. Some treatments may not be as efficient as they could be because they do not reduce the sleep complaints or even exacerbate the sleep disruption already present in depressed patients. Other treatments may be more efficient because they improve sleep.

3 Evidence for Sleep as a Causal Factor in Depression

The fact that sleep problems often precede the onset of depression is generally taken as an indication of a potential causal role of the sleep disturbances in the development of the mood disorder. Although one might argue that disrupted sleep perhaps only reflects some other underlying process that ultimately is responsible for both disturbed sleep and disturbed mood, there are several lines of evidence that support a causal role of disturbed sleep.

One line of evidence comes from before-mentioned studies suggesting that earlier parental-set bedtimes may act as a protective factor against depression and suicidal ideation in adolescents (Gangwisch et al. 2010). In this case, the relationship between sleep behavior and risk for depression is influenced by the parents

determining their children's bedtimes and sleep duration, which makes it less likely that the increased risk for depression is related to another underlying factor. Indeed, the relationship between bedtimes and risk for depression was largely explained by sleep duration and the perception of getting enough sleep. Importantly, a recent study showed that late bedtime and short sleep duration still significantly predicted subsequent development of depression after controlling for shared genetic and environmental factors in monozygotic twins (Matamura et al. 2014).

Other support for a causal role of disturbed sleep in the development or maintenance of depression comes from studies showing that treatment of sleep problems in itself may have a positive effect on mood in depressed patients and also enhance the response to pharmacological antidepressant treatments (Fava et al. 2006; Manber et al. 2008; Taylor et al. 2007). Taylor et al. (2007) used a repeated-measures design to compare the levels of insomnia and depression before and after 6 sessions of cognitive behavioral therapy that were aimed at improving sleep. Indeed, significant improvement in sleep was seen across the treatment period, with shorter sleep latency, longer total sleep, and higher sleep efficiency. This improvement persisted after the treatment. Importantly, a decreasing trend in depression scores was seen from pre- to post-treatment, which reached significance at a 3-month follow-up. In another study on patients suffering from major depression, antidepressant treatment with the selective serotonin reuptake inhibitor escitalopram was complemented with 7 sessions of behavioral therapy for insomnia over a period of 12 weeks (Manber et al. 2008). Behavioral therapy not only improved all actigraphy and diary measures of sleep, but it also enhanced depression outcome as compared to patients only treated with escitalopram without behavioral therapy. The effects of insomnia relief on mood in these studies were modest but clinically significant. One has to keep in mind, though, that sleep disturbance may gradually lead to changes in mood regulation that may no longer be simply reversible with subsequent enhancement of sleep. In other words, early treatment of sleep disorders may prevent the onset of a depression, but once a state of clinical depression is reached, treating sleep complaints may no longer be sufficient to fully reverse this.

Finally, while true experimental studies on chronically disrupted sleep and its possible contribution to the development of depression are not possible in humans for obvious ethical reasons, experimental studies performed in laboratory rodents have shown that chronically restricted sleep may gradually lead to neurobiological and neuroendocrine changes that are very similar to what has been reported for depressed patients, e.g., altered regulation of the hypothalamic–pituitary–adrenal axis (Meerlo et al. 2002; Novati et al. 2008), impaired serotonergic signaling (Roman et al. 2005a, 2006), and reduced hippocampal volume (Novati et al. 2011). Some of these changes appear to be rather persistent, even when the animals are allowed for unlimited recovery sleep (Roman et al. 2005a). Such experimental data provide strong support for the hypothesis that insufficient sleep in the long run may contribute to at least part of the symptoms of depression. Furthermore, animal studies may also provide clues to the potential mechanism underlying a causal relationship between sleep disruption and mood disorders.

4 Potential Mechanisms Underlying a Relationship Between Insufficient Sleep and Depression

Impaired sleep may increase the sensitivity to depression through a wide variety of different and possibly interacting mechanisms, all of which may ultimately affect brain plasticity and the regulation of cognitive functions and mood (Fig. 1).

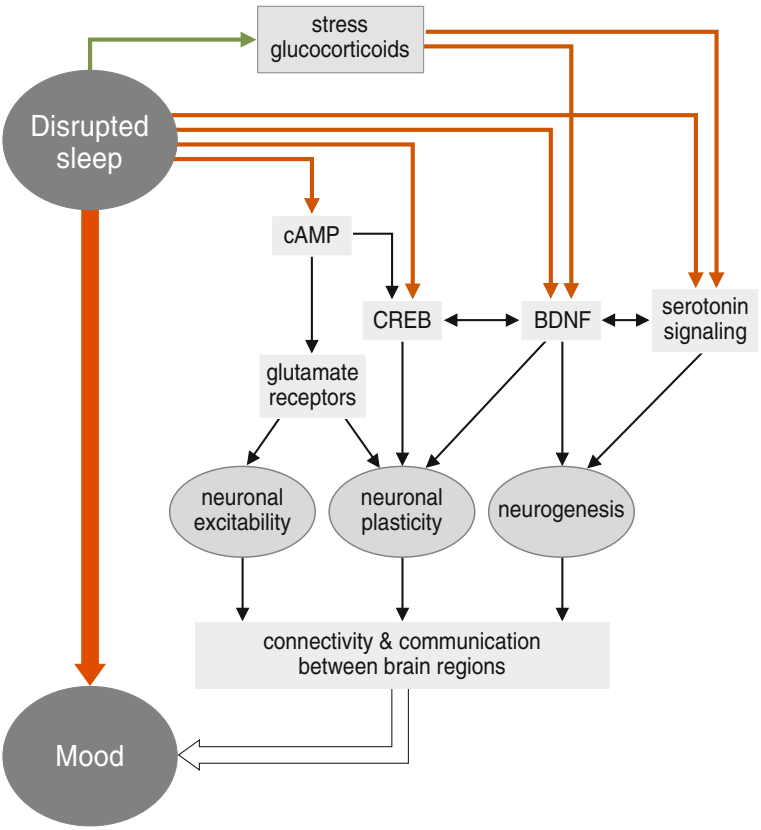

Fig. 1 Overview of potential mechanism through which chronically restricted and disrupted sleep may contribute to the development and maintenance of depression. *Green arrow* indicates a mild positive effect of restricted or disrupted sleep on neuroendocrine stress systems, which may result in elevated glucocorticoid levels. *Red arrows* indicate inhibitory effects on a variety of pathways, ultimately leading to a disturbance in connectivity and communication between brain regions involved in mood regulation (see text for details)

4.1 Stress and Glucocorticoids

Depression is often considered to be a disease of stress, not only because in many cases it is preceded by traumatic or stressful events, but also because the state of depression is frequently associated with an increased activity of neuroendocrine stress systems, particularly the hypothalamic–pituitary adrenal (HPA) axis. Various studies have described depression as a condition with HPA axis overactivity on the basis of elevated levels of hypothalamic corticotropin-releasing hormone and adrenal cortisol (e.g., Nemeroff et al. 1984; Gillespie and Nemeroff 2005).

Stress is also considered to be one of the major causes of sleep disturbance, and the latter may play an important role in the development of stress-related depression. In fact, even without external events triggering a state of stress, restricted or disrupted sleep may act as a stressor itself, both at the physiological and cognitive level.

At the physiological level, restricted or disrupted sleep may lead to a mild activation of the major neuroendocrine stress systems, including the HPA axis (for review, see Meerlo et al. 2008). Several controlled studies in humans have reported mild elevations of plasma cortisol levels associated with sleep deprivation (Chapotot et al. 2001; Leproult et al. 1997; Von Treuer et al. 1996). In most cases, the activation of the neuroendocrine systems during sleep deprivation is modest but may in subtle ways depend on the physical and mental activities subjects are engaged in (for review, see Meerlo et al. 2008). For instance, cortisol levels may rise during sleep deprivation when this is associated with sustained mental work (Radomski et al. 1992). The latter is highly relevant in real-life conditions, where people during sustained wakefulness often need to deal with all sorts of challenges.

At the cognitive level, insufficient sleep may dramatically alter the perception of the environment and the challenges that one is facing. Such challenges may then be perceived as more stressful than they would be under well-rested conditions. Indeed, a study in medical residents showed that sleep loss intensifies the negative emotional perception of disruptive and unforeseen events (Zohar et al. 2005). The latter has been confirmed in a controlled and experimental study showing that one night of sleep deprivation enhances negative emotional responses in a picture viewing task (Yoo et al. 2007).

Disrupted sleep may represent a state of stress particularly in cases where people have little control over their sleep, including sleep disorders such as insomnia. To many individuals that suffer from chronic sleep problems, the lack of sleep itself becomes a mental burden and a worrisome condition that may perhaps amplify the activation of neuroendocrine stress systems. This may be one factor contributing to the elevated levels of glucocorticoids reported in chronic insomniacs (Vgontaz et al. 2001).

The activation of the neuroendocrine stress systems as a consequence of restricted or disrupted sleep is often rather mild and may initially be considered a normal biological response that is aimed at supporting the metabolic demands of wakefulness. However, when disrupted sleep becomes a chronic condition, these

same stress hormones may contribute to central nervous system changes that gradually sensitize individuals to depression (Meerlo et al. 2008). For example, chronically elevated levels of glucocorticoid stress hormones may gradually reduce serotonergic receptor expression and impair serotonergic signaling in the brain (Karten et al. 1999; Meijer and De Kloet 1994). Elevated levels of glucocorticoids have also been associated with a reduction in hippocampal neurogenesis and hippocampal volume (Lucassen et al. 2010). Such changes in serotonergic signaling and hippocampal integrity may ultimately contribute to a disturbance in cognitive function and mood regulation (see sections below and Fig. 1).

4.2 Attenuated Serotonergic Neurotransmission

The serotonergic system in the brain is involved in the regulation of mood, and it has long been thought that an impairment of serotonergic neurotransmission may underlay the development and maintenance of depression (for reviews, see Cryan and Leonard 2000; Sobczak et al. 2002; Stockmeier 2003). Numerous studies have indicated an attenuated serotonin-1A receptor-mediated signaling in depression, as shown by blunted physiological responses to serotonin-1A agonists (Lesch 1991; Mann et al. 1995; Shapira et al. 2000) and a reduction in 1A binding capacity in PET studies (Drevets et al. 1999; Hirvonen et al. 2007; Sargent et al. 2000). Although postmortem studies have yielded varying results, some of them are consistent with a decrease in serotonin-1A receptor function in depression (for review, see Stockmeier 2003). Finally, antidepressant medication is often based on drugs that enhance serotonergic neurotransmission (Blier and de Montigny 1994; Middlemiss et al. 2002). Given this evidence for a role of the serotonergic system in clinical depression, a gradual alteration in serotonergic signaling seems a candidate mechanism by which disrupted and restricted sleep might increase the risk for this disease. Importantly, in one PET study on patients suffering from major depression, the lower serotonin-1A receptor binding capacity showed a particularly strong association with the occurrence of insomnia, thereby underscoring the relationship between sleep disturbance, depression, and changes in serotonergic neurotransmission (Hirvonen et al. 2007).

Experimental studies in laboratory rats have shown that chronic sleep restriction reduces serotonin-1A sensitivity (Roman et al. 2005a, 2006; Novati et al. 2008). In response to an injection of a 1A receptor agonist, sleep-restricted rats had a blunted temperature response (Roman et al. 2005a) and a blunted pituitary ACTH response (Novati et al. 2008), similar to what has been reported for depressed patients (Lesch 1991; Shapira et al. 2000). The desensitization of the serotonin-1A receptor system gradually developed over time. One or two nights of restricted sleep had no clear effect yet, but after a week of sleep restriction the serotonin-1A responses in rats were significantly reduced (Roman et al. 2005a; Novati et al. 2008). Importantly, the desensitization of the 1A system persisted for many days even with unlimited recovery sleep. In fact, after a week of restricted sleep, complete normalization of serotonin-1A receptor sensitivity almost required a similar

period of recovery (Roman et al. 2005a). Some effects of restricted sleep may thus be more persistent than is generally assumed.

As indicated in the previous section, a desensitization of the 1A receptor system as a consequence of insufficient sleep might be partly related to elevated glucocorticoid levels (Karten et al. 1999; Meijer and De Kloet 1994). However, in the rat studies, surgical removal of the adrenals, the main source of glucocorticoids, did not prevent the sleep restriction-induced desensitization of the 1A system, suggesting that other mechanisms are involved as well (Roman et al. 2006). The gradual desensitization of the serotonin-1A receptor system as a consequence of restricted sleep might in part be a consequence of serotonin itself, that is, a chronically enhanced serotonergic load on the receptors. Indeed, the release of serotonin is higher during wakefulness and sleep deprivation than it is during sleep (Park et al. 1999; Penalva et al. 2003) and continued or frequent stimulation of the receptors may gradually diminish their functional reactivity (Kreis and Lucki 1992; Li et al. 1999). Additionally, the desensitization of the serotonin-1A receptor population after chronic sleep restriction may be in part an indirect consequence of cross talk between this receptor system and other neurotransmitter systems such as the adenosine system. Adenosine is a metabolite of ATP, the main source of energy in the brain and body, and it is considered to be an important homeostatic molecule that signals neuronal activity and wakefulness (Basheer et al. 2004; Porkka-Heiskanen et al. 2002). Release of adenosine, and subsequent binding to its widespread G-protein-coupled A1 receptors, inhibits neuronal activity and promotes sleep, thereby protecting the brain against over activity. However, an increase in adenosine turnover under conditions of chronic sleep restriction and prolonged overstimulation of the receptors could result in desensitization, which might not only involve the receptors themselves but downstream elements of the signaling pathway as well. This could then affect the serotonin-1A receptor system because in various brain regions, adenosine A1 and serotonin-1A receptors are colocalized and share the G-proteins via which these receptors act on intracellular signaling cascades (Zgombick et al. 1989). A downregulation of the intracellular signaling pathways coupled to the adenosine A1 receptors might thus ultimately contribute to a reduction in serotonin-1A responses.

Reduced serotonergic signaling may be directly involved in disturbed mood (for reviews, see Cryan and Leonard 2000; Sobczak et al. 2002; Stockmeier 2003), but it may also impair plasticity processes, including neurotrophic signaling and neurogenesis, which in turn may affect neuronal circuitries involved in the regulation of mood (see next sections, Fig. 1).

4.3 Attenuated cAMP Signaling and Neuronal Plasticity

While depression was traditionally viewed as a neurochemical disorder, particularly a disorder of impaired and attenuated monoaminergic neurotransmission (i.e., serotonergic and noradrenergic signaling), this view has gradually shifted to depression

being a disorder associated with altered neuronal plasticity and neuronal connectivity (Castren et al. 2007; Duman 2002; Licznerski and Duman 2013; Nestler et al. 2002). This modern view is supported by findings of structural changes in the brains of depressed patients, regional reductions in the number of synapses and neurons, and alterations in signaling pathways that are crucially involved in plasticity processes (discussed in detail below).

At the basis of such altered neuronal plasticity might be an impaired regulation of the intracellular second messenger cyclic adenosine monophosphate (cAMP) and/or one of its downstream targets (Duman et al. 1997, 2002 . Cyclic AMP activates protein kinase A (PKA), which by means of phosphorylation controls the activity of various other downstream effector proteins. The latter includes phosphorylation and activation of the transcription factor cAMP response element-binding protein (CREB) that regulates the expression of a wide range of plasticity-related genes (Lonze and Ginty 2002).

Support for attenuated cAMP signaling and impaired regulation of neuronal plasticity in depression comes from analysis of postmortem brain samples of suicide victims showing reduced levels and activity of PKA and reduced levels of CREB in the prefrontal cortex and hippocampus (Dwivedi et al. 2003a, 2004). Moreover, antidepressant treatment stimulates components of the cAMP pathway. Particularly, expression of CREB was found to be increased in the hippocampus of depressed patients treated with antidepressant as compared to untreated patients (Dowlatshahi et al. 1998). Also in rodent models, treatment with various antidepressants was found to significantly increase mRNA and protein levels of CREB, phosphorylation of the CREB protein, and CREB-mediated gene transcription in several regions of the brain, including the cerebral cortex, hippocampus, and amygdala (e.g., Nibuya et al. 1996; Thome et al. 2000). This upregulation of CREB levels and activity only occurs with chronic, but not acute, treatment, in agreement with the slow onset of a therapeutic response in humans. Together, these findings suggest that at some level the regulation of the cAMP–PKA–CREB pathway may be impaired in depression and that reversal of this impairment may be a key in the treatment of the disorder (Blendy 2006; Duman et al. 1997; Duman 2002).

With respect to a potential role of insufficient sleep in this context, data on chronically restricted or disrupted sleep are limited, but consequences of acute sleep deprivation support a suppression of cAMP signaling in critical brain regions such as the hippocampus. Recent studies in mice have shown that brief sleep deprivation for only 5 h reduces cAMP levels in the hippocampus and thereby impairs plasticity processes and cognitive function (Vecsey et al. 2009; Havekes et al. 2014).

Such attenuated cAMP–PKA signaling as a consequence of sleep loss may directly affect phosphorylation and thereby the expression of glutamate receptor subunits at the cell membrane, which in turn determines neuronal excitability and the strength of neuronal connections. Indeed, studies in rats have shown that sleep deprivation for 6–12 h reduces hippocampal glutamate AMPA receptor phosphorylation (Hagewoud et al. 2010). A reduction in AMPA receptor phosphorylation and function has also been reported after multiple days of sleep

disruption (Ravassard et al. 2009). Other studies have reported reduced hippocampal glutamate NMDA receptor surface expression after prolonged sleep deprivation of 24–72 h (Chen et al. 2006; McDermott et al. 2006). In agreement with these findings are several studies reporting that sleep deprivation impairs the induction of hippocampal long-term potentiation, which depends in part on glutamate receptors (e.g., Campbell et al. 2002; Chen et al. 2006; Marks and Wayner 2005; McDermot et al. 2006; Vescey et al. 2009).

Additionally, impaired cAMP–PKA signaling as a consequence of sleep loss may result in lower levels of CREB phosphorylation and activity, which is supported by studies in laboratory rodents showing that brief sleep deprivation for only 5–6 h can attenuate basal levels of CREB phosphorylation in the hippocampus (Vescey et al. 2009) and may also attenuate the increase in CREB phosphorylation normally associated with learning and memory processes (Alhaider et al. 2011, Hagewoud et al. 2011). While fairly brief sleep deprivation is capable of reducing phosphorylation and activity of CREB in the hippocampus, prolonged 48-h sleep deprivation or fragmentation was even found to reduce basal levels of CREB expression (Guzman-Marín et al. 2006).

Among the many genes, of which the expression is under control of CREB, are several genes that give rise to growth factors and neurotrophic factors, including brain-derived neurotrophic factor (BDNF) (Lonze and Ginty 2002). In rats, prolonged sleep deprivation or fragmentation was found to cause a reduction in BDNF mRNA and protein levels, in parallel to a reduction in CREB expression (Guzman-Marin et al. 2006). BDNF is an important promoter of neurogenesis, neuronal survival, and synaptic plasticity (Huang and Reichardt 2001; Park and Poo 2013). While reduced BDNF signaling in itself may not result in depression directly, it may impair plasticity processes and thereby alter connectivity within networks of brain regions involved in the regulation of mood (Castren et al. 2007; Nestler et al. 2002). In agreement with this are findings of reduced mRNA and/or protein levels of BDNF in the hippocampus and prefrontal cortex of suicide subjects (Dwivedi et al. 2003b). Moreover, antidepressant medication appears to restore BDNF levels to a normal range. Expression of BDNF was found to be increased in the hippocampus of depressed patients treated with antidepressant as compared to untreated patients (Dowlatshahi et al. 1998; Chen et al. 2001).

Importantly, BDNF often works in concert with serotonin to regulate gene expression and neuronal plasticity processes (Martinowich and Lu 2008; Mattson et al. 2004). Moreover, the BDNF and serotonin signaling systems mutually affect each other (Martinowich and Lu 2008). BDNF can stimulate the growth and plasticity of serotonergic neurons (Mamounas et al. 1995) and, conversely, enhanced serotonergic signaling through antidepressant medication promotes BDNF expression (Nibuya et al. 1996). These reciprocal interactions and the finding that both BDNF and serotonergic signaling may be impaired by prolonged sleep restriction add to the complexity of potential mechanism through which insufficient sleep may lead to impaired brain function and altered mood regulation.

4.4 Hippocampal Neurogenesis

It has been hypothesized that depression may in part result from a suppression of hippocampal neurogenesis and that successful antidepressant treatment requires an enhancement of neurogenesis (Eisch and Petrik 2012; Jacobs et al. 2000; Lucassen et al. 2010; Sahay and Hen 2007). One popular argument in favor of the neurogenic hypothesis is the common finding that depressed patients have a reduced hippocampal volume, which might in part be explained by lower levels of neurogenesis (see next section). Secondly, chronic treatment with antidepressants has been found to increase hippocampal cell proliferation in humans (Boldrini et al. 2012) and animals (Czéh et al. 2001; Malberg et al. 2000; Santarelli et al. 2003).

In recent years, various studies in laboratory rodents have examined how the production of new cells and their development into neurons is affected by sleep deprivation or sleep fragmentation (for review, see Meerlo et al. 2009). While interfering with sleep for a period shorter than a day appears to have little effect on the basal rate of cell proliferation, prolonged restriction or disruption of sleep may have cumulative effects leading to a major decrease in hippocampal cell proliferation, cell survival, and neurogenesis(e.g., Guzman-Marin et al. 2007; Mueller et al. 2008; Roman et al. 2005b; for review see Meerlo et al. 2009).

Hippocampal neurogenesis is regulated and affected by a wide variety of molecular factors, including trophic factors, cytokines, hormones, and a range of neuromodulators and neurotransmitters (Abrous et al. 2005; Ming and Song 2005). Some of these factors are also modulated by sleep deprivation or sleep disruption and may therefore provide a link between insufficient sleep and reduced neurogenesis (Fig. 1).

The effect of restricted or disrupted sleep on neurogenesis might be driven in part by stress hormones, particularly glucocorticoids, which have been found to suppress cell proliferation and survival (Wong and Herbert 2004, 2005). However, a number of controlled studies in rats showed that blocking glucocorticoid effects by means of adrenalectomy did not prevent the reduction in cell proliferation seen with 4–7 days of sleep fragmentation or partial sleep deprivation (Guzman-Marin et al. 2007; Mueller et al. 2008; for a critical discussion, see Meerlo et al. 2009). Alternatively, the effect of insufficient sleep on neurogenesis could be caused in part by reduced serotonergic signaling. The generation of new cells in the hippocampus is promoted by serotonin via the serotonin-1A receptor (Banasr et al. 2004; Radley and Jacobs 2002), and restricted sleep gradually desensitizes the 1A receptor system (Novati et al. 2008; Roman et al. 2005). The reduction in serotonin-1A sensitivity with sleep curtailment is not immediately evident but only develops in the course of prolonged sleep restriction, which is in agreement with the finding that suppression of hippocampal cell proliferation does not occur after short sleep deprivation but only after prolonged sleep deprivation. Moreover, also BDNF facilitates hippocampal cell proliferation and survival (Lee et al. 2002; Scharfman et al. 2005) and hippocampal expression of BDNF was found to be reduced after 48 h of sleep deprivation (Guzman-Marin et al. 2006).

Ultimately, the mechanisms by which chronically restricted or disrupted sleep reduces hippocampal neurogenesis may involve a complex and interacting set of factors, and some of these factors may selectively affect different stages of the neurogenic process, from cell proliferation to differentiation and maturation, to incorporation of new neurons in the existing hippocampal network. Because newly generated neurons are thought to play an important role in hippocampal function, and ultimately the regulation of cognitive function and emotion, a reduction of neurogenesis as a consequence of disrupted sleep may explain some of the symptoms of depression (Meerlo et al. 2009).

4.5 Structural Changes in the Brain

Several postmortem and imaging studies have reported structural changes in the brains of depressed patients, particularly reductions in the volume of the hippocampus (Campbell et al. 2004; Videbech and Ravnkilde 2004) and subregions of the prefrontal cortex (Rajkowska et al. 1999; Drevets 2000). In the prefrontal cortex, this reduction in volume is associated with a decrease in the size and density of both glia cells and neurons (Rajkowska et al. 1999), and a reduction in the number of synapses (Kang et al. 2012). Similar cellular changes may underlie the reduction in hippocampal volume, but this has not been unequivocally proven (Czeh and Lucassen 2007). Additionally, a smaller hippocampus might be partly the result of reduced neurogenesis (Czeh and Lucassen 2007; Lucassen et al. 2010). Both the hippocampus and prefrontal cortex are important parts of the brain network that regulates cognitive functions and mood, and the molecular or cellular changes underlying the volume reduction may explain the key symptoms of depression (Drevets 2000; Licznerski and Duman 2013).

Importantly, structural changes in the very same brain regions have also been reported in patients suffering from insomnia, i.e., reduced gray matter in prefrontal cortex subregions (Altena et al. 2010; Joo et al. 2013) and a smaller hippocampus (Neylan et al. 2010; Riemann et al. 2007; Joo et al. 2014). A number of studies suggest that, in particular, smaller hippocampi correlate with the severity or duration of insomnia (Neylan et al. 2010; Noh et al. 2012) and also with poorer cognitive function in a variety of tasks, including verbal and visual memory (e.g., Noh et al. 2012; Joo et al. 2014). Not all studies were able to replicate these findings, which might be due to the heterogeneity and age of the study population, as well as variation in insomnia duration and severity (Noh et al. 2012; Spiegelhalder et al. 2013).

A reduction in hippocampal volume has also been reported for other sleep disorders such as sleep apnea (Morrell et al. 2003) and narcolepsy (Joo et al. 2012). Moreover, in healthy children, a significant positive correlation was found between hippocampal volume and habitual sleep duration on weekdays (Taki et al. 2012).

While in humans it is difficult to assess whether subtle differences in brain structure are causally related to sleep duration or sleep disturbance, a recent

experimental study in rats suggests this may be the case (Novati et al. 2011). Rats subjected to a schedule of sleep restriction allowing them only 4 h of sleep per day for a period of a month, as compared to the usual 10 h per day, had a 10 % decrease in hippocampal volume. This decrease could not be fully explained by a reduction in neurogenesis and may have been caused by other cellular changes, which might include neuronal shrinkage, dendritic atrophy, and loss of synapses as a result of impaired cAMP–PKA–CREB signaling and neurotrophic signaling discussed in previous sections. Additionally, a reduction in hippocampal volume might be related to reductions in the number and size of glia cells. Evidence is limited, but in one rat study proliferation of cells that were presumed to give rise to glia was reduced in response to sleep deprivation (Roman et al. 2005b), while another study suggested that proliferation of specific oligodendrocyte precursor cells was reduced (Bellesi et al. 2013).

Together, the findings presented in this section support the hypothesis that structural changes in the brain of depressed patients may at least be partly a result of chronically disrupted sleep.

5 Brain Region-Specific Consequences of Disrupted Sleep

Remarkably, the literature discussed in previous sections strongly suggests that among the brain regions that most frequently display structural and functional abnormalities in depressed patients are also the ones that appear to suffer most from inadequate sleep, particularly the prefrontal cortex and the hippocampus. This parallel may imply a general vulnerability of these brain regions to any kind of disturbance, but it also supports the view that disrupted sleep plays a causal role in the structural and functional changes that are seen in depression.

One obvious example of regional variation in sensitivity to the consequences of insufficient sleep is the reported suppression of neurogenesis (Meerlo et al. 2009), which in adulthood is largely restricted to the hippocampus (Abrous et al. 2005; Ming and Song 2005). Also other aspects of hippocampal plasticity and function appear to be more sensitive to sleep loss than is the case for some other brain regions. For example, neurotrophic signaling may be more severely affected in the hippocampus than in some other parts of the brain, as demonstrated by a study in rats reporting a suppression of BDNF after prolonged 48-h sleep disturbance in the hippocampus but not the neocortex (Guzmán-Marín et al. 2006). Moreover, multiple days of sleep disturbance prior to acquisition impairs subsequent hippocampus-dependent contextual fear conditioning but not amygdala-mediated tone-cued fear conditioning (McDermott et al. 2003; Ruskin et al. 2004). In humans, a single night of mild sleep disruption was found to attenuate hippocampal activation and subsequent memory in a hippocampus-dependent declarative task, while it had no effect on a hippocampus-independent memory task (Van der Werf et al. 2009). Together, these findings clearly demonstrate that insufficient sleep has a negative effect on plasticity processes and cognitive function particularly when it involves the hippocampus.

Because the consequences of disrupted sleep may vary between brain regions, this may alter the connectivity and communication between the regions that are most affected and the ones that are more resistant. Such may contribute to an unbalanced activity in brain networks involved in the regulation of mood and thereby ultimately contribute to mood disorders.

6 Conclusions and Future Perspectives

Depression is a complex disorder that most likely is the result of various interacting factors such as sensitive genes, developmental environment, lifestyle, and adult stress. Mounting data suggest that restricted or disrupted sleep may be an important causal factor as well. The mechanisms underlying such a relationship between insufficient sleep and depression may include activation of neuroendocrine stress systems and altered serotonergic signaling. Additionally, chronically insufficient sleep might contribute to depression through negative effects on signaling pathways involved in neuronal plasticity and neurogenesis. Clearly, as sleep is considered to play a crucial role in regulating neuronal plasticity and synaptic strength, chronically insufficient sleep may very well contribute to depression through a gradually developing impairment of the way neuronal networks in the brain are organized. The fact that, for reasons not understood, some brain regions are more sensitive to sleep loss than others may contribute to a disbalance in connectivity and communication between areas involved in mood regulation.

In recent years, major advances have been made in our understanding of the role of sleep in neuronal plasticity and the molecular consequences of acute sleep loss, which provide a framework for hypotheses on the mechanisms underlying the relationship between disrupted sleep in mood disorders. Yet, there is still a paucity of experimental data on the molecular and cellular consequences of insufficient sleep as a chronic condition, as it often occurs in real life. Many of the changes in plasticity processes that have been reported occur after fairly brief sleep deprivation and often normalize after subsequent recovery sleep. Future studies are required to assess, one, whether more chronically restricted or disrupted sleep has similar and perhaps more persistent effects on neuronal plasticity, and two, whether the consequent alterations in plasticity signaling contribute to changes in mood regulation.

Another topic that requires attention is the obvious individual differences in the consequences of insufficient sleep and subsequent risk for depression. Not all individuals that regularly experience insufficient sleep or suffer from sleep disturbance become depressed. Perhaps restricted and disrupted sleep significantly contributes to the development of depression particularly in individual with specific genotypes, or perhaps insufficient sleep contributes to depression particularly when it interacts with other environmental factors and stressors.

With respect to the treatment of depression, more studies are required that focus on the potential role of sleep and sleep disturbances in the efficacy and long-term outcome of antidepressant medication. Many of the current antidepressants do not

improve sleep or may even exacerbate existing sleep problems, which can have a negative impact on the outcome of the treatment and the course of the disease (Emslie et al. 2012; Hatzinger et al. 2004; Pigeon et al. 2008). More research efforts should be devoted to, one, developing antidepressant medications that normalize sleep and two, developing additional therapies that may aid in the improvement of sleep such as behavioral therapy or physical exercise (Brand et al. 2010; Manber et al. 2008; Taylor et al. 2007).

Finally, a major issue that needs to be resolved is the paradox of sleep deprivation therapy. Evidence is accumulating that chronically insufficient sleep may be causal factor that increases the risk for depression; yet, on the other hand, once people are depressed, many of them respond positively to a night of sleep deprivation (Benedetti et al. 2007; Giedke and Schwarzler 2002; Wirz-Justice and Van den Hoofdakker 1999). Although this phenomenon seems contradictory in the context of proposed causal role of insufficient sleep in the development of mood disorders, it also underscores the importance of sleep-related processes in the regulation and dysregulation of mood.

References

Abrous DN, Koehl M, Le Moal M (2005) Adult neurogenesis: from precursors to network and physiology. Physiol Rev 85:523–569

Agargun MY, Kara H, Solmaz M (1997) Sleep disturbances and suicidal behavior in patients with major depression. J Clin Psychiatry 58:249–251

Alhaider IA, Aleisa AM, Tran TT, Alkadhi KA (2011) Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. Mol Cell Neurosci 46:742–751

Altena E, Vrenken H, Van Der Werf YD, van den Heuvel OA, Van Someren EJ (2010) Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. Biol Psychiatry 67:182–185

Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, Lombardo C, Riemann D (2011) Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Aff Disorders 135:10–19

Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacol 29:450–460

Banks S, Dinges DF (2007) Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med 3:519–528

Basheer R, Strecker RE, Thakkar MM, McCarley RW (2004) Adenosine and sleep-wake regulation. Prog Neurobiol 73:379–396

Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C (2013) Effects of sleep and wake on oligodendrocytes and their precursors. J Neurosci 33:14288–14300

Benca RM, Peterson MJ (2008) Insomnia and depression. Sleep Med 9(Suppl 1):S3–S9

Benedetti F, Barbini B, Colombo C, Smeraldi E (2007) Chronotherapeutics in a psychiatric ward. Sleep Med Rev 11:509–522

Bernert RA, Joiner TE Jr, Cukrowicz KC, Schmidt NB, Krakow B (2005) Suicidality and sleep disturbances. Sleep 28:1135–1141

Blendy J (2006) The role of CREB in depression and antidepressant treatment. Biol Psychiatry 59:1144–1150

Blier P, de Montigny C (1994) Current advances and trends in the treatment of depression. Trends Pharmacol Sci 15:220–226

Boldrini M, Hen R, Underwood MD, Rosoklija GB, Dwork AJ, Mann JJ, Arango V (2012) Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. Biol Psychiatry 72:562–571

Bonnet MH, Arand DL (1995) We are chronically sleep deprived. Sleep 18:908–911

Brand S, Gerber M, Beck J, Hatzinger M, Pühse U, Holsboer-Trachsler E (2010) Exercising, sleep-EEG patterns, and psychological functioning are related among adolescents. World J Biol Psychiatry 11:129–140

Breslau N, Roth T, Rosenthal L, Andreski P (1996) Sleep disturbance and psychiatric disorders: longitudinal epidemiological study of young adults. Biol Psychiatry 39:411–418

Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rossler W (2008) Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep 31:473–480

Campbell IG, Guinan MJ, Horowitz JM (2002) Sleep deprivation impairs long-term potentiation in rat hippocampal slices. J Neurophysiol 88:1073–1076

Campbell S, Marriott M, Nahmias C, MacQueen GM (2004) Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 161:598–607

Castren E, Voikar V, Rantamaki T (2007) Role of neurotrophic factors in depression. Curr Opin Pharmacol 7:18–21

Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ (1997) Insomnia in young men and subsequent depression. The Johns Hopkins precursors study. Am J Epidemiology 1997 (146):105–114

Chapotot F, Buguet A, Gronfier C, Brandenberger G (2001) Hypothalamo-pituitary-adrenal axis activity is related to the level of central arousal: effects of sleep deprivation on the association of high-frequency waking electroencephalogram with cortisol release. Neuroendocrinology 73:312–321

Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001) Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50:260–265

Chen C, Hardy M, Zhang J, LaHoste GJ, Bazan NG (2006) Altered NMDA receptor trafficking contributes to sleep deprivation-induced hippocampal synaptic and cognitive impairments. Biochem Biophys Res Commun 340:435–440

Cryan JF, Leonard BE (2000) 5-HT1A and beyond: the role of serotonin and its receptors in depression and the antidepressant response. Hum Psychopharmacol Clin Exp 15:113–135

Czéh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E (2001) Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci USA 98:12796–12801

Czéh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? Eur Arch Psychiatry Clin Neurosci 257:250–260

Dowlatshahi D, MacQueen GM, Wang JF, Young LT (1998) Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. Lancet 352:1754–1755

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C (1999) PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 46:1375–1387

Drevets WC (2000) Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog Brain Res 126:413–431

Duman RS, Heninger GR, Nestler EJ (1997) A molecular and cellular theory of depression. Arch Gen Psychiatry 54:597–606

Duman RS (2002) Pathophysiology of depression: the concept of synaptic plasticity. Eur J Psychiatry 17(suppl 3):306–310

Dwivedi Y, Rao JS, Rizavi HS, Kotowski J, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2003a) Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. Arch Gen Psychiatry 60:273–282

Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2003b) Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 60:804–815

Dwivedi Y, Rizavi HS, Shukla PK, Lyons J, Faludi G, Palkovits M, Sarosi A, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2004) Protein kinase A in postmortem brain of depressed suicide victims: altered expression of specific regulatory and catalytic subunits. Biol Psychiatry 55:234–243

Eisch AJ, Patrik D (2012) Depression and hippocampal neurogenesis: a road to remission? Science 338:72–75

Emslie GJ, Kennard BD, Mayes TL, Nakonezny PA, Zhu L, Tao R, Hughes C, Croarkin P (2012) Insomnia moderates outcome of serotonin-selective reuptake inhibitor treatment in depressed youth. J Child Adolesc Psychopharmacol 22:21–28

Fava M, McCall WV, Krystal A, Wessel T, Rubens R, Caron J, Amato D, Roth T (2006) Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol Psychiatry 59:1052–1060

Fitzgerald CT, Messias E, Buysse DJ (2011) Teen sleep and suicidality: results from the youth risk behavior surveys of 2007 and 2009. J Clin Sleep Med 7:351–356

Ford DE, Kamerow DB (1989) Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? J Am Med Assoc 262:1479–1484

Gangwisch JE, Babiss LA, Malaspina D, Turner JB, Zammit GK, Posner K (2010) Earlier parental set bedtimes as a protective factor against depression and suicidal ideation. Sleep 33:97–106

Giedke H, Schwarzler F (2002) Therapeutic use of sleep deprivation in depression. Sleep Med Rev 6:361–377

Gillespie CF, Nemeroff CB (2005) Hypercortisolism and depression. Psychosom Med 67:S26–S28

Goodwin RD, Marusic A (2008) Association between short sleep and suicidal ideation and suicide attempt among adults in the general population. Sleep 31:1097–1101

Gregory AM, Caspi A, Eley TC, Moffitt TE, Oconnor TG, Poulton R (2005) Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. J Abnorm Child Psychol 33:157–163

Gregory AM, Rijsdijk FV, Lau JYF, Dahl RE, Eley TC (2009) The direction of longitudinal associations between sleep problems and depression symptoms: a study of twins aged 8 and 10 years. Sleep 32:189–199

Guzman-Marin R, Ying Z, Suntsova N, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation. J Physiol 575:807–819

Guzman-Marin R, Bashir T, Suntsova N, Szymusiak R, McGinty D (2007) Hippocampal neurogenesis is reduced by sleep fragmentation in the adult rat. Neuroscience 148:325–333

Hagewoud R, Havekes R, Novati A, Keijser JN, Van der Zee EA, Meerlo P (2010) Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. J Sleep Res 19:280–288

Hagewoud R, Bultsma L, Koolhaas JM, Meerlo P (2011) Sleep deprivation impairs contextual fear conditioning and attenuates subsequent behavioral, endocrine and neuronal responses. J Sleep Res 20:259–266

Hatzinger M, Hemmeter UM, Brand S, Ising M, Holsboer-Trachsler E (2004) Electroencephalographic sleep profiles in treatment course and long-term outcome of major depression: association with DEX/CRH-test response. J Psychiatr Res 38:453–465

Havekes R, Bruinenberg VM, Tudor JC, Ferri SL, Baumann A, Meerlo P, Abel T (2014) Transiently increasing cAMP levels selectively in hippocampal excitatory neurons during sleep deprivation prevents memory deficits caused by sleep loss. J Neurosci 34:15715–15721

Hirvonen J, Karlsson H, Kajander J, Lepola A, Markkula J, Rasi-Hakala H, Nagren K, Salminen JK, Hietala J (2007) Decreased brain serotonin 5-HT1A receptor availability in medication-naïve patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-C]WAY-100635. Int J Neuropsychopharmacol 11:465–476

Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677–736

Jacobs BL, Praag H, Gage FH (2000) Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 5:262–269

Joo EY, Kim SH, Kim ST, Hong SB (2012) Hippocampal volume and memory in narcoleptics with cataplexy. Sleep Med 13:396–401

Joo EY, Noh HJ, Kim JS, Koo DL, Kim D, Hwang KJ, Kim JY, Kim ST, Kim MR, Hong SB (2013) Brain gray matter deficits in patients with chronic primary insomnia. Sleep 36:999–1007

Joo EY, Kim H, Suh S, Hong SB (2014) Hippocampal substructural vulnerability to sleep disturbance and cognitive impairment in patients with chronic primary insomnia: magnetic resonance imaging morphometry. Sleep 37:1189–1198

Kang HJ, Voleti B, Hajszan T, Rajkowska G, Stockmeier CA, Licznerski P, Lepack A, Majik MS, Jeong LS, Banasr M, Son H, Duman RS (2012) Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat Med 18:1413–1417

Karten YJG, Nair SM, Van Essen L, Sibug R, Joels M (1999) Long-term exposure to high corticosterone levels attenuates serotonin responses in rat hippocampal CA1 neurons. Proc Natl Acad Sci 96:13456–13461

Kreiss DS, Lucki I (1992) Desensitization of 5-HT1A autoreceptors by chronic administration of 8-OH-DPAT. Neuropharmacology 31:1073–1076

Lee J, Duan W, Mattson MP (2002) Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 82:1367–1375

Lee YJ, Cho SJ, Cho IH, Kim SJ (2012) Insufficient sleep and suicidality in adolescents. Sleep 35:455–460

Leproult R, Copinschi G, Buxton O, Van Cauter E (1997) Sleep loss results in an elevation of cortisol levels the next evening. Sleep 20:865–870

Lesch KP (1991) 5-HT1A receptor responsivity in anxiety disorders and depression. Prog Neuropsychopharmacol Biol Psychiatry 15:723–733

Li Q, Wichems C, Heils A, Van de Kar LD, Lesch KP (1999) Reduction of 5-hydroxytriptamine (5-HT) 1A-mediated temperature and neuroendocrine responses and 5-HT1A binding sites in 5-HT transporter knockout mice. J Pharm Exp Ther 291:999–1007

Licznerski P, Duman RS (2013) Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. Neurosci 251:33–50

Liu X, Buysse DJ (2005) Sleep and youth suicidal behavior: a neglected field. Curr Opp Psychiat 19:288–293

Liu X, Buysse DJ, Gentzler AL, Kiss E, Mayer L, Kapornai K, Vetro A, Kovacs M (2007) Insomnia and hypersomnia associated with depressive phenomenology and comorbidity in childhood depression. Sleep 30:83–90

Lonze BE, Ginty DD (2002) Function and regulation of CREB family transcription factors in the nervous system. Neuron 35:605–623

Lucassen PJ, Meerlo P, Naylor AS, Van Dam AM, Dayer AG, Fuchs E, Oomen CA, Czeh B (2010) Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action. Eur Neuropsychopharmacol 20:1–17

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110

Mallon L, Broman JE, Hetta J (2000) Relationship between insomnia, depression, and mortality: a 12-year follow-up of older adults in the community. Int Psychogeriatr 12:295–306

Mamounas LA, Blue ME, Siuciak JA, Altar CA (1995) Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. J Neurosci 15:7929–7939

Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T (2008) Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. Sleep 31:489–495

Mann JJ, McBride PA, Malone KM, DeMeo M, Keilp J (1995) Blunted serotonergic responsivity in depressed inpatients. Neuropsychopharmacology 13:53–64

Marks CA, Wayner MJ (2005) Effects of sleep disruption on rat dentate granule cell LTP in vivo. Brain Res Bull 66:114–119

Martinowich K, Lu B (2008) Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacol 33:73–88

Matamura M, Tochigi M, Usami S, Yonehara H, Fukushima M, Nishida A, Togo F, Sasaki T (2014) Associations between sleep habits and mental health status and suicidality in a longitudinal survey of monozygotic twin adolescents. J Sleep Res 23:290–294

Mattson MP, Maudsley S, Martin B (2004) BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci 27:589–594

McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003) Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J. Neurosci 23:9687–9695

McDermott CM, Hardy MN, Bazan NG, Magee JC (2006) Sleep deprivation-induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. J Physiol 570: 553–565

Meerlo P, Koehl M, Van der Borght K, Turek FW (2002) Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. J Neuroendocrinol 14:397–402

Meerlo P, Sgoifo A, Suchecki D (2008) Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev 12:197–210

Meerlo P, Mistlberger RE, Jacobs BL, Heller HC, McGinty D (2009) New neurons in the adult brain: the role of sleep and consequences of sleep loss. Sleep Med Rev 13:187–194

Meijer AM, Habekothe HT, Van-Den Wittenboer GL (2000) Time in bed, quality of sleep and school functioning of children. J Sleep Res 9:145–153

Meijer OC, De Kloet ER (1994) Corticosterone suppresses the expression of 5-HT1A receptor mRNA in rat dentate gyrus. Eur J Pharmacol 266:255–261

Middlemiss DN, Price GW, Watson JM (2002) Serotonergic targets in depression. Curr Opin Pharmacol 2:18–22

Ming G, Song H (2005) Adult neurogenesis in the mammalian central nervous system. Annu Rev Neurosci 28:223–250

Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR (2003) Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 4:451–454

Mueller AD, Pollock MS, Lieblich SE, Epp JR, Galea LA, Mistlberger RE (2008) Sleep deprivation can inhibit adult hippocampal neurogenesis independent of adrenal stress hormones. Am J Physiol 294:R1693–R1703

Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W (1984) Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 226:1342–1344

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002) Neurobiology of depression. Neuron 34:13–25

Neylan TC, Mueller SG, Wang Z, Metzler TJ, Lenoci M, Truran D, Marmar CR, Weiner MW, Schuff N (2010) Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. Biol Psychiatry 68:494–496

Nibuya M, Nestler EJ, Duman RS (1996) Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J Neurosci 16:2365–2372

Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D, Lee GH, Hong SB (2012) The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. J Clin Neurol 8:130–138

Novati A, Roman V, Cetin T, Hagewoud R, Den Boer JA, Luiten PG, Meerlo P (2008) Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. Sleep 31:1579–1585

Novati A, Hulshof HJ, Koolhaas JM, Lucassen PJ, Meerlo P (2011) Chronic sleep restriction causes a decrease in hippocampal volume in adolescent rats that is not explained by changes in glucocorticoid levels or neurogenesis. Neuroscience 190:145–155

Park SP, Lopez-Rodriguez F, Wilson CL, Maidment N, Matsumoto Y, Engel J Jr (1999) In vivo microdialysis measures of extracellular serotonin in the rat hippocampus during sleep-wakefulness. Brain Res 833:291–296

Park H, Poo MM (2013) Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 14:7–23

Penalva RG, Lancel M, Flachskamm C, Reul JMHM, Holsboer F, Linthorst ACE (2003) Effect of sleep and sleep deprivation on serotonergic neurotransmission in the hippocampus: a combined in vivo microdialysis/EEG study in rats. Eur J Neurosci 17:1896–1906

Pigeon WR, Hegel M, Unutzer J, Fan MY, Sateia MJ, Lyness JM, Phillips C, Perlis ML (2008) Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort? Sleep 31:481–488

Pigeon WR, Pinquart M, Conner K (2012) Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J Clin Psychiat 73:e1160–e1167

Porkka-Heiskanen T, Alanko L, Kalinchuk A, Stenberg D (2002) Adenosine and sleep. Sleep Med Rev 6:321–332

Radley JJ, Jacobs BL (2002) 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res 955:264–267

Radomski MW, Hart LE, Goodman JM, Plyley MJ (1992) Aerobic fitness and hormonal responses to prolonged sleep deprivation and sustained mental work. Aviat Space Environ Med 63:101–106

Rajaratnam SMW, Arendt J (2001) Health in a 24-h society. The Lancet 358:999–1005

Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA (1999) Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 45:1085–1098

Ravassard P, Pachoud B, Comte JC, Mejia-Perez C, Scoté-Blachon C, Gay N, Claustrat B, Touret M, Luppi PH, Salin PA (2009) Paradoxical (REM) sleep deprivation causes a large and rapidly reversible decrease in long-term potentiation, synaptic transmission, glutamate receptor protein levels, and ERK/MAPK activation in the dorsal hippocampus. Sleep 32:227–240

Riemann D, Voderholzer U (2003) Primary insomnia: a risk factor to develop depression? J Aff Disord 76:255–259

Riemann D, Voderholzer U, Spiegelhalder K, Hornyak M, Buysse DJ, Nissen C, Hennig J, Perlis ML, van Elst LT, Feige B (2007) Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. Sleep 30:955–958

Roane BM, Taylor DJ (2008) Adolescent insomnia as a risk factor for early adult depression and substance use. Sleep 31:1351–1356

Roberts RE, Duong HA (2013) Depression and insomnia among adolescents: a prospective perspective. J Affect Disord 148:66–71

Roman V, Walstra I, Luiten PG, Meerlo P (2005a) Too little sleep gradually desensitizes the serotonin 1A receptor system in rats. Sleep 28:1505–1510

Roman V, Van der Borght K, Leemburg SA, Van der Zee EA, Meerlo P (2005b) Sleep restriction by forced activity reduces hippocampal cell proliferation. Brain Res 1065:53–59

Roman V, Hagewoud R, Luiten PGM, Meerlo P (2006) Differential effects of chronic partial sleep deprivation and stress on serotonin-1A and muscarinic acetylcholine receptor sensitivity. J Sleep Res 15:386–394

Ruskin DN, Liu C, Dunn KE, Bazan NG, LaHoste GJ (2004) Sleep deprivation impairs hippocampus-mediated contextual learning but not amygdala-mediated cued learning in rats. Eur. J. Neurosci 19:3121–3124

Sahay A, Hen R (2007) Adult hippocampal neurogenesis in depression. Nature Neurosci 10:1110–1115
Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805–809
Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ (2000) Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635. Arch Gen Psychiatry 57:174–180
Shapira B, Newman ME, Gelfin Y, Lerer B (2000) Blunted temperature and cortisol responses to ipsapirone in major depression: lack of enhancement by electroconvulsive therapy. Psychoneuroendocrinology 25:421–438
Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S (2005) Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 192:348–356
Sobczak S, Honig A, Van Duinen MA, Riedel WJ (2002) Serotonergic dysregulation in bipolar disorders: a literature review of serotonergic challenge studies. Bipolar Disord 4:347–356
Spiegelhalder K, Regen W, Baglioni C, Klöppel S, Abdulkadir A, Hennig J, Nissen C, Riemann D, Feige B (2013) Insomnia does not appear to be associated with substantial structural brain changes. Sleep 36:731–737
Stockmeier CA (2003) Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. J Psychiatr Res 37:357–373
Taki Y, Hashizume H, Thyreau B, Sassa Y, Takeuchi H, Wu K, Kotozaki Y, Nouchi R, Asano M, Asano K, Fukuda H, Kawashima R (2012) Sleep duration during weekdays affects hippocampal gray matter volume in healthy children. Neuroimage 60:471–475
Taylor DJ, Lichstein KL, Weinstock J, Sanford S, Temple JR (2007) A pilot study of cognitive-behavioral therapy of insomnia in people with mild depression. Behav Ther 38:49–57
Thome J, Sakai N, Shin K, Steffen C, Zhang YJ, Impey S, Storm D, Duman RS (2000) cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. J Neurosci 20:4030–4036
Van den Bulck J (2004) Television viewing, computer game playing, and Internet use and self-reported time to bed and time out of bed in secondary-school children. Sleep 27:101–104
Van der Werf YD, Altena E, Schoonheim MM et al (2009) Sleep benefits subsequent hippocampal functioning. Nature Neurosci 12:122–123
Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, Huang T, Brown KM, Li XY, Descalzi G, Kim SS, Chen T, Shang YZ, Zhuo M, Houslay MD, Abel T (2009) Sleep deprivation impairs cAMP signalling in the hippocampus. Nature 461:1122–1125
Vgontaz AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP (2001) Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 86:3787–3794
Videbech P, Ravnkilde B (2004) Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 161:1957–1966
Von Treuer K, Norman TR, Armstrong SM (1996) Overnight human plasma melatonin, cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep recovery. J Pineal Res 20:7–14
Wirz-Justice A, Van den Hoofdakker RH (1999) Sleep deprivation therapy in depression: what do we know, where do we go? Biol Psychiat 46:445–453
Wong EY, Herbert J (2004) The corticoid environment: a determining factor for neural progenitors' survival in the adult hippocampus. Eur J Neurosci 20:2491–2498
Wong EY, Herbert J (2005) Roles of mineralocorticoid and glucocorticoid receptors in the regulation of progenitor proliferation in the adult hippocampus. Eur J Neurosci 22:785–792
Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP (2007) The human emotional brain without sleep: a prefrontal amygdala disconnect. Curr Biol 17:877–878

Zgombick JM, Beck SG, Mahle CD, Craddock-Royal B, Maayani S (1989) Pertussis toxin-sensitive guanine nucleotide-binding protein(s) couple adenosine A1 and 5-hydroxytryptamine 1A receptors to the same effector systems in rat hippocampus: biochemical and electrophysiological studies. Mol Pharmacol 35: 484–494

Zohar D, Tzischinsky O, Epstein R, Lavie P (2005) The effects of sleep loss on medical resident' emotional reactions to work events: a cognitive-energy model. Sleep 28:47–54

Sleep Deprivation Therapy for Depression

Sara Dallaspezia and Francesco Benedetti

Abstract Sleep deprivation (SD) is the most widely documented rapid-onset antidepressant therapy, targeting the broadly defined depressive syndrome. Although SD responses are transient, its effects can be sustained by concomitant medications (e.g., selective serotonin reuptake inhibitors and lithium) and circadian-related interventions (e.g., bright light and sleep phase advance). Thus, considering its safety, this technique can now be considered among the first-line antidepressant treatment strategies for patients affected by mood disorders. SD is a complex intervention and it should be considered multi-target in nature. Thus, the mechanisms explaining its antidepressant effect can be looked for on many levels, involving not only monoaminergic mechanisms but also sleep homeostatic and circadian mechanisms, glutamatergic mechanisms and synaptic plasticity.

Keywords Mood disorder · Depression · Antidepressant therapy · Chronotherapeutics · Sleep deprivation

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1 Sleep Deprivation Therapy for Depression

Maintaining stable sleep-wake cycles is of central importance to the maintenance of stability in mood disorder in particular in Bipolar Disorder, and insomnia is a strong risk factor for subsequent depression. However, once patients are depressed, manipulation of their sleep has often been reported to improve or normalize mood.

Schulte (1971) first suggested that sleep deprivation (SD) might benefit depressed patients. He based this suggestion on anecdotal reports from three depressed patients who "treated" themselves with SD, a teacher who bicycled an entire night, another teacher who was able to go through an exam period by staying awake all night, and a physician who stayed awake every 2 or 3 nights. Schulte's great contribution was to take these reports seriously and to prompt his collaborators Pflug and Tölle to carry out systematic investigations thereof. Since first being described in the 1970s, the antidepressant effect of SD has been replicated in numerous studies, and during more than 40 years, literally thousands of patients have been treated with this antidepressant technique. Despite not already being considered a first-line treatment like all chronobiological interventions, SD has been widely used because its rapid antidepressant efficacy is highly reproducible and substantial (Bunney and Bunney 2013), and it makes SD a potential first-line treatment for depression. Initially, its use had been restricted to experimental settings aimed at increasing knowledge about the pathophysiology of mood disorders by studying the mechanisms of action of this treatment. Indeed, the application in common clinical practice was discouraged by the observation that SD generally caused a transient antidepressant effect with most of patients showing a relapse after a night of recovery sleep, even when a complete response had been achieved the evening before (Leibenluft and Wehr 1992). In recent years, the development of new clinical strategies has led to the possibility to sustain the effects of SD over time and to achieve sustained euthymia by combining different chronobiological techniques (e.g., SD plus light therapy) or by combining SD with antidepressant drugs and mood stabilizers (Wirz-Justice et al. 2009). Nowadays, SD is used by many psychiatrists and it could be considered one of the most rapid antidepressants available today (Wirz-Justice et al. 2005).

1.1 Response Rate and Predictors of Response

It is still unclear how many hours of SD are needed to achieve its full antidepressant effect. The minimum amount of sleep restriction needed to obtain antidepressant effects has not been determined, but very short SD schedules, such as a 2 h of SD in the middle of the night between 3 a.m. and 5 a.m. have been shown to produce little clinical effects (Giedke et al. 1990). The typical antidepressant SD is called "total" SD (TSD) because the patient is kept awake throughout the night of treatment. It begins with the extension of daytime wake into the night and lasts about 36 h until the evening of the day after. Variants of TSD are selective REM-SD (Vogel et al. 1975), whose antidepressant efficacy after positive early reports has not been replicated (Grozinger et al. 2002), and partial sleep deprivation (PSD), during which sleep is allowed during one-half of the night (Grozinger et al. 2002). Concerning PSD, although clinicians routinely restrict sleep to the first half of the night, unequivocal superiority of this strategy to allow sleep in this part of the night has not been shown (Giedke et al. 1992). Actually, the effects of total SD are best documented in the literature compared to those of other sleep restriction modalities.

The influence of SD on mood strictly depends on the presence of a mood disorder. Indeed, healthy subjects and patients affected by psychiatric disorders other than depression, such as obsessive-compulsive disorder (Joffe and Swinson 1988) or panic disorder (Roy-Byrne et al. 1986), experience no changes or a worsening of mood after SD. Within the heterogenous population of depressed patients, SD antidepressant effects have been described in many depressive conditions, such as endogenous unipolar, bipolar and schizoaffective depression, reactive depression, depression in the elderly, depression associated with pregnancy or the postpartum period, premenstrual dysphoric disorder, and depression secondary to Parkinson's disease or schizophrenia (Benedetti et al. 2007a). However, when comparing clinical conditions, the antidepressant efficacy of the chronobiological treatment was greater in endogenous primary depression compared to reactive and/or secondary depression (Vogel et al. 1975). Moreover, the therapeutic effect seems to be proportional to the patient's susceptibility to develop mania, with bipolar patients showing higher response rates than unipolar ones (Barbini et al. 1998).

The reported response rates to SD are similar to those observed with antidepressant drugs, ranging from 50 to 80 % of treated patients, with a meanresponse rates of 60 % of treated patients across all diagnostic subgroups (Wirz-Justice and Van den Hoofdakker 1999). Whereas antidepressant drugs show long response latencies, response to SD becomes clinically relevant in a matter of hours after the beginning of treatment (i.e., the day after).

There are several know predictors of the response to SD therapy. First, the effect seems to be linked to individual timing of physiological and behavioral rhythms (Selvi et al. 2007). In fact, alteration in the phase of biological rhythms observed in mood disorders have been presumed to be required for the antidepressant effect not only of SD but also of antidepressant drugs (Benedetti et al. 2009). Moreover, the

diurnal variation of mood observed during major depression predicts antidepressant response to SD, with the patients who show the typical diurnal mood fluctuation with an evening mood improvement benefiting more from the chronobiological treatment than other patients (Martiny et al. 2013; Reinink et al. 1990).

Patient sleep characteristics prior to SD may also influence response to treatment. However, contradictory results were found: In some investigations, patients with short sleep time, low sleep efficiency, and little slow-wave sleep responded better to SD, but other researchers found the opposite or no relationship (Giedke and Schwarzler 2002). Similarly, contradictory findings are with REM latency and REM density (Giedke and Schwarzler 2002). One study found a correlation between delta sleep and antidepressant effect of SD, with a high delta sleep ratio (quotient of slow-wave activity in the first to the second NREM episode) being a positive predictor for response to treatment (Nissen et al. 2001).

Other predictors of response to SD besides diagnosis and diurnal mood fluctuations have been reported. An abnormal dexamethasone suppression test (DST) result was found to be a positive predictors of response, with clinical response being more favorable in these patients who had a trend for normalization of the test after the treatment (Kasper et al. 1983). The levels of interleukin-6, whose production is known to be enhanced in patients affected by a major depressive episode, were found to be linked with response to SD with lower levels before treatment being associated with better response (Benedetti et al. 2002). Moreover, levels of neurotransmitter metabolites in urine and cerebrospinal fluid indicate that low peripheral sympathetic activity and high central noradrenergic activity favor response to SD (Kuhs and Tolle 1991).

Imaging studies found a difference in cerebral cortex activation in specific areas between responder and nonresponder patients. Indeed, depressed patients who had a favorable clinical response to SD were shown to have higher relative metabolic rates in the ventral anterior cingulate, medial prefrontal cortex, and posterior subcallosal cortex at baseline than either normal volunteers or depressed patients who did not respond to SD (Wu et al. 1999). Significant decreases in metabolic rates occurred after treatment in the medial prefrontal cortex and frontal pole in the patients who responded positively to SD (Wu et al. 1999).

Finally, SD antidepressant effects were found to be influenced by the same functional polymorphisms that affect the efficacy of antidepressant drugs (Benedetti et al. 2009). In particular, significant associations have been observed with gene variants affecting the promoter of the serotonin transporter (Benedetti et al. 1999b), the serotonin receptor 2A (Benedetti et al. 2008b), the catechol-O-methyltransferase (Benedetti et al. 2010), and the glycogen synthase kinase-3b promoter (Benedetti et al. 2004a, b). Moreover, in a recent research, gene–gene interactions between components of the monoaminergic signal transduction pathways and of plasticity-related pathways, such as serotonin transporter and glycogen synthase kinase-3b, were found to influence response to SD (Benedetti et al. 2011), with a gene promoter polymorphism which reduces the activity of GSK3-beta counteracting the detrimental influence of the short form of the serotonin transporter promoter on antidepressant response.

1.2 Exclusion Criteria and Contraindication

Sleep is a potent activator of interictal epileptiform discharges, and SD is a trigger of epileptic seizures. Indeed, the only established contraindication to SD is the presence of epilepsy, because of the high risk of seizure induction linked to sleep reduction (Demet et al. 1999). However, literature evidence suggests caution in administering SD in particular groups of patients.

There are few studies of SD in patients affected by Parkinson's disease. SD is associated with a marked increase in dopaminergic neurotransmission. This increase could explain the temporary improvement in motor scores shown by patients affected by Parkinson's disease after both total (Demet et al. 1999) and partial (Hogl et al. 2001) SD which was associated with a more prolonged amelioration of depressive symptoms (Bertolucci et al. 1987). In different subgroups of patients, however, both sleep benefit and worsening of symptomatology after SD have been reported (Demet et al. 1999). Caution should then be used in administering antidepressant SD to patients affected by the disease. The presence of psychotic symptoms should be carefully evaluated. Indeed, even if patients affected by delusional depression were found to react more favorably than nonpsychotic depressives to total SD combined with clomipramine, they also showed a larger negative response after recovery sleep (either unlimited or partial sleep) compared with other patients (Demet et al. 1999). Moreover, anecdotal reports about the use of SD in delusional depression showed that in some cases after the treatment, there was a worsening of overall symptomatology including an increased extension and pressure of delusions as rated on Dimensions of Delusional Experience Rating Scale (Benedetti et al. 1999c; Fahndrich 1981). In the absence of balanced controlled trials, no definite conclusions can be drawn on this topic, but caution and a careful antipsychotic strategy is suggested by the available literature.

Patients on depot neuroleptics have been demonstrated to have a lesser antidepressant response to SD. Thus, if possible, a complete washout is suggested before the beginning of the treatment (Demet et al. 1999).

Even if partial SD has been successfully used to treat depression during pregnancy, when the use of psychotropic drugs is discouraged (Parry et al. 2000), a history of sleep disruption in the latter stages of pregnancy has been associated with the development of postnatal blues (Demet et al. 1999). Since it is not clear if this sleep alteration is an early symptom of the postpartum depressive syndrome or has a role in its pathogenesis, caution should be suggested in administering SD, as any other stressor, to pregnant women.

Finally, although SD is generally well tolerated, the nonspecific stress associated with staying awake all night could unexpectedly precipitate unsuspected medical conditions, e.g., undetected severe cardiovascular diseases (Delva et al. 2001; Suh et al. 2007). Thus, a medical examination aimed at ruling out the presence of medical conditions that can be worsened by even low degrees of stress is suggested before the beginning of the treatment.

1.3 Safety

Sleep deprivation has very few side effects, and three alternate nights awake have been found safe in several studies (Colombo et al. 1999; Smeraldi et al. 1999). The most common and obvious adverse effect of sleep restriction is daytime sleepiness with the degree of sleepiness showing a high individual variability.

In bipolar patients, there have been occasional reports of switches into hypomania or mania. The risk of a manic switch after therapeutic SD seems to be low, preventable, and is usually easily treated. Current data show an approximate 5 % switch rate into mania and 6 % into hypomania. The switch rate is decreased by the concomitant use of mood-stabilizing drugs but is increased to 10–15 % of patients with a concomitant use of antidepressant drugs. The switch rate is similar to those observed with SSRIs and placebo, lower than those reported with tricyclic antidepressants (Peet 1994), and much lower than those reported (10–29 %) in bipolar patients receiving antidepressant drugs as maintenance treatment (Frye et al. 2009). Moreover, the severity of mania induced by TSD is mild or moderate in the majority of patients. Indeed, less than half of patients need to combine antipsychotic medication with mood stabilizers to return to euthymia and one-third of switch patients, who get a good night of recovery sleep (facilitated by benzodiazepines), return to euthymia without any further treatment (Wirz-Justice et al. 2009).

If patients have comorbid panic disorder, they should be informed that panic attacks will be expected to worsen during the night of SD. However, this will not reduce response to the chronobiological treatment (Wirz-Justice et al. 2009).

1.4 Short-Term Relapses and Augmentation Therapies

The clinical usefulness of SD treatment has been questioned by the short duration of its antidepressant effects: The therapeutic response can vanish as fast as it develops. Indeed, after recovery sleep up to 80 % of SD-responders relapse (though mostly not completely), only a minority of patients maintain the achieved improvement (Giedke and Schwarzler 2002). In the following days, patients show a trend of progressive worsening and the severity of depression most often returns to the same levels observed at baseline (Leibenluft and Wehr 1992). Approximately 10–15 % of patients do not improve after the night of SD, but show an atypical improvement in the day following the recovery night of sleep (Giedke et al. 1992). In this case, the achieved improvement tends to progressively deteriorate in the following days.

Over the years, many strategies have been studied and developed to prevent this short-term relapse and to sustain the effects of SD over time. Recent trials have shown that depression relapse can be prevented by combining SD with other chronobiological treatments, with lithium salts, or with antidepressant drugs.

Repetition of SD treatment was initially unsuccessful. Indeed, not only a tolerance to the therapeutic effects was found (Roy-Byrne and Uhde 1984), but also,

following eventual discontinuation, patients usually showed a relapse with only 5–10 % of treated patients maintaining stable euthymia if no augmentation therapy was used (Benedetti et al. 1999a).

Antidepressant SD has been successfully combined with different antidepressant drugs, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and with the dopaminergic amineptine in a synergistic way (Benedetti et al. 2011). Lithium salts as well have been found to sustain the antidepressant effect of SD. Moreover, ongoing lithium mood stabilizer therapy was found to enhance the response to the chronobiological treatment, probably by overcoming the effect of unfavorable genetic predispositions which affect the functioning of the serotoninergic system (Benedetti et al. 2008a).

Early relapse after SD can also be prevented by combining it with other chronobiological treatment such as light therapy (LT) or sleep phase advance. Early studies on SD and light showed that the beneficial effects of SD became clinically relevant when patients were exposed to morning light (Wehr et al. 1985). Moreover, not only the exposure to bright LT during and after wake therapy was shown to stabilize the antidepressant effect of both partial (Neumeister et al. 1996) and repeated total SD (Colombo et al. 2000), but also the use of bright light during SD was demonstrated to generate a more prolonged improvement of responders (van den Burg et al. 1990).

In a similar way, sleep phase advance has been shown to prevent the early relapse after SD. According to this strategy proposed by Berger et al. (1997), after one day of TSD, patients go to bed early, at 5 p.m. for a 7-h sleep until midnight; in this way, an acute 6-h phase advance of sleep is imposed. Then, the original nocturnal sleep time is re-obtained by slowly shifting the sleep schedule back by 1 h each day until a sleep time of 11:00 p.m. to 6:00 a.m. is reached.

Two further studies have demonstrated maintenance of the clinical response to SD, with advanced sleep phase (17–24 h) better than a normal (23–06 h) or delayed sleep period (02–09 h) (Riemann et al. 1996, 1999). With SPA not only positive TSD responses can be preserved in 60 ± 75 % of the cases but also some patients who do not show a response to TSD alone obtain an antidepressant effect.

A treatment schedule which is effective in preventing short-term relapses has been developed by our group, based on repeated SD combined with bright LT and lithium salts (Colombo et al. 2000). It lasts one week and it consists of three cycles of 36-h SD separated by one night of recovery sleep sleep. On the first, third, and fifth day, patients stay awake from 7 a.m. until 7 p.m. the following day. They are then allowed to sleep during the night of the second, fourth, and sixth day. Repeated SD therapy on alternate days does not imply severe sleep loss. The alternation with three nights of undisturbed sleep means that the period of sleep–wake cycle is increased from the usual 24 h length to 48 h. SD is carried out in normal ambient light, but patients are administered LT (10,000 lux light for half an hour) during the SD night at 3 a.m. and in the morning after recovery sleep sleep at around 8–9 a.m., half an hour after awakening. If patients are not being treated with ongoing lithium salts, they start them at the beginning of the chronotherapeutic procedure. Moreover, the add-on of repeated TSD + LT to continued antidepressant medication and lithium

was also found to be useful in the treatment of drug-resistant bipolar patients, with an acute antidepressant response in the 44 % of patients who did not show a response to antidepressant drug (Benedetti et al. 2005a).

2 Brain Imaging of Sleep Deprivation: Effects in Specific Brain Areas

Specific effects of SD on the brain have been found by different brain imaging studies showing an association between response to SD and functional and metabolic changes in specific brain areas.

In particular, responders to the chronobiological treatment have been reported to show an increased relative localized metabolic activity in the ventral/anterior cingulate cortex compared with nonresponders or normal controls at baseline. A better antidepressant effect is correlated with higher baseline activity levels and a greater decrease induced by the treatment. The metabolic changes after SD are paralleled by a decrease in perfusion of cingulate (Clark et al. 2006) and amygdala (Clark et al. 2006), which is specific of response to treatment and by changes in neural correlates of brain activity in response to tasks targeting the typical depressive negative cognitive distortions (Benedetti et al. 2007b). Moreover, a single proton magnetic resonance spectroscopy study by our group found a correlation between changes in spectroscopic correlates of glutamatergic activity in the cingulate cortex and response to SD (Benedetti et al. 2009).

The ventral/anterior cingulate cortices implicated in the detection of response errors and conflict, and detection of unfavorable outcomes and decision uncertainty (Ridderinkhof et al. 2004). Moreover, the activity in the cingulate cortex during perceptual processing of fearful stimuli has been demonstrated by blood-oxygen-level-dependent-functional magnetic resonance imaging to be coupled with that of limbic structures, contributing to feedback circuits implicated in the extinction of negative affect (Pezawas et al. 2005) and in providing a neural basis for mood congruent cognitive biases in depression (Elliott et al. 2002). Changes of neural activity in these areas can be postulated to be a correlate of depression and of depression recovery, and have been shown after response to both antidepressant drugs and SD (Benedetti et al. 2007b; Davidson et al. 2003). Thus, changes in brain metabolism paralleling successful antidepressant can be considered very similar irrespective of the treatment strategy. However, there is a difference in the temporal frame needed to obtain them according to the antidepressant treatment: one day for SD, several weeks for drugs.

3 Proposed Mechanisms of Action

Hypotheses about the way SD works also have implications about the nature of depression and the function of sleep, which are both unsolved questions. Literature often considers "unknown" the mechanism of action of SD which has multiple effects: This is because researchers do not agree on which of the multiple and powerful effects of chronotherapeutics on the brain, all involving targets for psychiatric antidepressant treatment, are responsible for the clinical mood amelioration. Most probably, all these mechanisms contribute to the clinical outcome.

3.1 Sleep Homeostatic and Circadian Mechanisms

Changes in sleep homeostasis have been hypothesized to play a major role in the mechanism of action of SD (Wirz-Justice and Van den Hoofdakker 1999). The two process model of sleep regulation postulates an interaction of a homeostatic process S and a circadian process C. Sleep need is represented by process S and is reflected in EEG slow-wave activity. Sleep onset and sleep termination are determined by the level of S and by a gating system consisting of two thresholds under control of the circadian process C (Clark et al. 2006). According to the S-deficiency model, during depression, there is a deficient build-up of the homeostatic process with process C remaining unaffected (Borbely and Wirz-Justice 1982); SD is supposed to be therapeutic because the level of process S is transiently increased to normal. This early hypotheses based on the two process model of sleep regulation links to the recent "synaptic homeostasis hypothesis" of sleep (Tononi and Cirelli 2003). According to this model, while during wakefulness, plastic processes lead to an increase in synaptic strength in many brain circuits, during sleep that synaptic strength is downscaled to baseline levels through a breakdown in cortical effective connectivity (Massimini et al. 2005). Recent studies in humans confirmed that the slope and amplitude of the early electroencephalography response to transcranial magnetic stimulation, which is a measure of the cortical excitability, steadily increased during prolonged wakefulness, thus paralleling homeostatic sleep pressure (Hanlon et al. 2011), and decreased after sleep (Huber et al. 2013). In a recent study, Canali et al. (2014) found that the circadian pattern of progressive increase of cortical excitability during wake was absent in bipolar depressed patients, in agreement with current perspectives on impaired sleep homeostasis in bipolar disorder (Harvey 2008) and in animal models of depression (Savelyev et al. 2012). When considering TSD, bipolar patients showed a sawtooth pattern of increased cortical excitability during wake and decreased during sleep with measures of synaptic strength being markedly higher in responder subjects at baseline, despite a similar pattern of variation in responders and nonresponders during treatment. Since changes of synaptic strength during the sleep/wake cycle suggest that SD is associated with synaptic potentiation (Bushey et al. 2011; Tononi and Cirelli 2006),

these findings could let surmise that the progressive enhancement in cortical excitability after SD in bipolar depression may capture changes of synaptic efficiency and neuroplasticity. Moreover, considering that cortical excitability has been proposed as a correlate of process S, these findings then confirm hypotheses of process S increase as a core mechanism of action of antidepressant SD.

It has been hypothesized that the mechanism of antidepressant action of SD involves resetting abnormal circadian clock gene machinery and that the commonly seen relapse in symptoms following the recovery sleep night of sleep is caused by reactivation of the clock gene abnormalities (Bunney and Bunney 2013). SD can influence the activity of the suprachiasmatic nucleus (SCN) of the hypothalamus by modifying vigilance state transitions and sleep states (Deboer et al. 2003). Surprisingly, very little data are available on this topic, and the only clinical finding being a correlation reported between positive antidepressant response to SD and advance of the activity–rest circadian cycle (Benedetti et al. 2007c). Moreover, recently SD was found to influence the expression of some genes of the biological clock which are known to contribute to the homeostatic aspect of sleep regulation (Bunney and Bunney 2013). In the mouse cerebral cortex, sleep loss was shown to reduces the DNA binding of BMAL1, CLOCK, and NPAS2 resulting in an increasing of Per2 expression in the cortex (Mongrain et al. 2011). These data are in agreement with the finding that acute SD under light conditions (constant environmental conditions with a maximum light intensity of 50 lux) influenced Per2 expression in human peripheral blood mononuclear cells (Kavcic et al. 2011).

3.2 Monoaminergic Mechanisms

The synergistic interaction between SD and antidepressant drugs observed in clinical studies supported a major role for monoamines in the mechanism of action for SD, and neurobiological studies in human subjects and in animal models have shown that SD was able to increase the activity of all the neurotransmitter systems targeted by antidepressant drugs: serotonin (5-HT), norepinephrine (NE), and dopamine (DA) (Kavcic et al. 2011). Biological factors affecting the activity of these pathways, such as genotypic variants (Benedetti et al. 1999b 2003a, b, 2007b, 2008a, b), basal neurotransmitter levels (Gerner et al. 1979), or the extent of receptor occupancy (Ebert et al. 1994), affect the clinical response, thus confirming a critical role for changes in monoaminergic neurotransmission in the clinical effect of SD. Moreover, an interplay between monoaminergic systems in response to antidepressant drugs nominally acting on a single system was found and could involve the recognition, uptake, storage, and release of different monoamines by the same membrane transmitter uptake systems (Sulzer and Edwards 2005).

Brain NE receptors show a circadian rhythm, and the lack of sleep was shown to increase synaptic levels of NE (Hipolide et al. 2005), and tyrosine hydroxylase and NE transporter mRNA in the locus coeruleus (Basheer et al. 1998), where during REM sleep NE discharge is absent (Siegel and Rogawski 1988). This NE discharge

during SD was thought to explain its effects (Payne et al. 2002; Wirz-Justice et al. 1981). Despite interest in early studies, showing that NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (Amin et al. 1980) and MHPG sulfate (Muller et al. 1993) increased after SD proportionally to severity of depression and clinical response to treatment (Matussek et al. 1977), there is a lack of knowledge about the clinical relevance of changes in NE signaling after SD.

Results consistently supported the hypothesis of a major role for an enhancement in 5-HT neurotransmission in the behavioral effects of SD in major depression with an increase in serotonergic function seeming to be required for the antidepressant effect of the treatment. In particular, changes in the activity of brain 5-HT pathways after SD (Adrien 2002) include an increase in serotonergic neuronal activity in the dorsal raphe nucleus (Gardner et al. 1997), an increase in brain 5-HT turnover (Asikainen et al. 1997), an increase in extracellular 5-HT (Lopez-Rodriguez et al. 2003), and an increase in behavioral responsiveness to 5-HT precursors both in animal models (Santos and Carlini 1983) and in depressed humans (Salomon et al. 1994), with a reduction in sensitivity of 5-HT1A inhibitory autoreceptors. In patients, not only has the clinical effect of SD been demonstrated to be enhanced and sustained by the concomitant use of serotoninergic drugs (Benedetti et al. 1997), but also it was found that the administration of pindolol, a 5-HT1A-β adrenoreceptor blocking drug, enhanced the antidepressant efficacy of the chronobiological treatment in bipolar subjects (Smeraldi et al. 1999). Moreover, several pharmacogenetic studies have confirmed the influence of a polymorphism in the promoter gene for the 5-HT transporter (5-HTTLPR), previously reported to be associated with an antidepressant response to serotonergic treatments ADD reference, on antidepressant efficacy of SD as well (Serretti et al. 2005), suggesting that SD shares the neurobiological mechanisms of action of drugs targeting the 5-HT system. 5-HTTLPR shows a 44 base pairs insertion/deletion functional polymorphism, with the deletion being associated with reduced transcriptional efficiency and decreased expression of 5-HT transporter protein (Heils et al. 1997). This polymorphism influences in the same direction and with similar effect sizes, the antidepressant response to the 5-HT uptake inhibitors and to SD alone or combined with LT, with the short variant homozygotes showing worse response rates to treatments (Serretti et al. 2005). This negative genetic influence can be overcome by a concomitant long-term lithium treatment (Benedetti et al. 2008a).

Also, two imaging studies have suggested associations between 5-HTTLPR and antidepressant effects of drug and SD treatments. Using iodine-123-labeled 2beta-carbomethoxy-3beta-(4-iodophenyl)-tropane single photon emission computerized tomography, homozygote carriers of the long alleles showed a higher 5-HTT occupancy in diencephalon and midbrain associated with better clinical improvement (Ruhe et al. 2009). Moreover, in a BOLD fMRI study, baseline activations in dorsolateral prefrontal cortex and dorsal anterior cingulate cortex of depressed bipolar patients correlated both with antidepressant response to SD and with 5-HTTLPR genotype (Benedetti et al. 2007b). Since dorsolateral prefrontal cortex and anterior cingulate cortex have been demonstrated to interact with serotonergic nuclei and environmental stimuli in the generation and control of depressed mood

(Hamann 2005; Robbins 2005), these studies suggest that the rapid changes in 5-HT function, which parallel the increase in mood caused by SD, lead to changes in the gene-modulated functioning of brain structures involved in the cognitive generation of affect.

Another genetic polymorphism in the serotoninergic system, a functional polymorphism in the 5HT2A receptor gene, was found to influence the antidepressant response to SD. All genotype groups showed the same response rate after the night of SD but T homozygotes, showing an higher cortical 5HT2A receptor binding potential, showed greater benefits after the 5HT2A sleep (Benedetti et al. 2008a, b).

Clinically, the antidepressant effect of SD was shown to be influenced by the dopaminergic drug amineptine (Benedetti et al. 1996, 2001). Moreover, other evidences of the clinical relevance of the role of DA come from the only negative interaction of SD with antidepressant drugs, which has been reported when SD was combined with trimipramine (Holsboer-Trachsler et al. 1994), a drug which shows in vitro DA antagonistic properties (Grunze et al. 1999). Sound neurobiological data link SD effects to an enhancement of DA activity. Changes in the activity of the DA system after SD were shown both in animal models and human beings. After SD, rodents not only showed an increased behavioral response to DA agonists (Mogilnicka 1981; Tufik et al. 1978) in different experimental settings but DA antagonists were also shown to block the behavioral effects of sleep loss (Gessa et al. 1995). Moreover, SD was found to affect dopamine receptor subtypes in mouse striatum with a decrease in D1 Receptor, no change in D2 Receptor, and a significant increase in D3 Receptor binding (Lim et al. 2011).

In humans, lower spinal fluid homovanillic acid before SD correlated with better response to the chronobiological treatment (Gerner et al. 1979), suggesting that basal turnover of DA and activity of the DA system predict response to this DA-stimulating intervention. A DA hyperactivity during SD is suggested also by the finding of a decrease in plasma levels of prolactin, which is inhibited by DA agonists (Baumgartner et al. 1990; Kasper et al. 1988), and an increase in eye-blink rate (Ebert et al. 1996) after SD. The effects of SD on dopamine activity have recently been studied in the human brain using positron emission tomography with [11C]raclopride, which targets D2 and D3receptors (Volkow et al. 2008). [11C] raclopride binding was significantly reduced in the striatum and thalamus in healthy subjects after one night of SD compared with rested sleep. However, when authors compared subjects given placebo or methylphenidate after one night of SD (Volkow et al. 2012), the dopamine increase induced by methylphenidate (measured as decreases in D2/D3 receptor availability compared with placebo) did not differ between rested sleep and SD, and was associated with increased alertness and reduced sleepiness when methylphenidate was administered after SD. The authors postulated that these findings are consistent with a downregulation of D2/D3 receptors in ventral striatum. Moreover, direct evidence of a major role for DA activation in influencing antidepressant response to SD come from the consistent results of SPECT brain imaging studies using the benzamide derivate 123I-3-iodo-methoxybenzamide (IBZM) as a radioligand competing with endogenous DA for

D2 receptor occupancy. In bipolar depressed subjects treated with SD and ongoing amitriptyline, D2 receptor occupancy in the right basal ganglia is similar in patients before the chronobiological treatment and unaffected controls, but it significantly decreased in responders to SD compared with nonresponders, suggesting an enhanced dopamine release in responders (Ebert et al. 1994). Unfortunately, methodological limitations did not allow identification of changes in SPECT DA binding outside the basal ganglia and did not then allow determination of the role of DA function in cortical regions.

Even if different studies showed negative effects of functional gene variants influencing DA D2, D3, and D4 receptor signaling (Benedetti et al. 2003b; Serretti et al. 1999), a recent study found that a functional polymorphism in catechol-O-methyltransferase, which inactivates dopamine via methyl conjugation, influences antidepressant response to SD combined with light therapy. Indeed, patients homozygote for the allelic variant link to an higher inactivation of dopamine show a less efficient antidepressant effect of the chronobiological treatment (Benedetti et al. 2010).

3.3 Glutamatergic Mechanisms and Synaptic Plasticity

Recently, the SD mechanism of action has been suggested to involve glutamate and glycogen synthase kinase 3-β (GSK 3-β) as well. Glutamate is the primary excitatory neurotransmitter of the human brain, and glutamate signaling is involved in brain development and synaptic plasticity, both of which are modified in individuals affected by bipolar disorder, and have been implicated in the etiology of the disorder (Manji et al. 2003). SD was found to alter glutamate metabolism with a reduction in cortical glutamate concentrations measured by a single voxel, single proton magnetic resonance spectroscopy paralleling clinical response to the chronobiological treatment in patients affected by bipolar depression (Benedetti et al. 2009). Remarkably, the effects were detected in dorsal anterior cingulate cortex, where changes in 5-HT function were found to influence neural response to depressive cognitive stimuli (Benedetti et al. 2007b). Moreover, mGluR5 receptor availability, which is reduced during depression, was found to be increased after a single night without sleep in healthy subjects (Hefti et al. 2013). These findings thus suggest a role for Glu neurotransmission, and its interaction with monoamines, in the rapid antidepressant effects of SD.

GSK3-β is an essential element of Wnt/beta-catenin pathway, which is involved in the control of gene expression, cell behavior, cell adhesion, and cell polarity, and plays major roles in neurodevelopment and in regulation of neuronal plasticity and cell survival (Kavcic et al. 2011). Moreover, GSK3-β is supposed to be involved in the mechanism of action of lithium and serotonergic antidepressants and its Drosophila orthologue SHAGGY was found to be implicated in the regulation of the molecular clock located in the SCN of the hypothalamus (Kavcic et al. 2011). A promoter single nucleotide polymorphism of GSK3-β (−50 T/C; rs334558) has been associated with transcriptional strength in vitro (greater activity of the T allele)

(Kwok et al. 2005). Homozygote carriers of the low-activity C allele were found to show less detrimental clinical features of mood disorders, including a delayed onset of illness (Benedetti et al. 2004a, b) and a better clinical response to lithium salts both in the prevention of illness recurrences (Benedetti et al. 2005a, b) and in the augmentation therapy of drug-resistant depressive episodes (Adli et al. 2007). This polymorphism influenced, in the same direction, acute antidepressant response to SD, with bipolar depressed homozygote carriers of the C allele showing better mood amelioration after the night awake and a relapse similar to the other subjects after recovery sleep (Benedetti et al. 2004a, b). Recently, rs334558 was found to counteract the detrimental influence of the short form of the 5-HT promoter on antidepressant response to SD (Benedetti et al. 2011). This finding is in agreement with previous research in animal models, where SD not only increased monoaminergic neurotransmission (Benedetti et al. 2009), but it also promoted a synaptic potentiation increasing the inhibitory phosphorylation of GSK3-β (Vyazovskiy et al. 2008).

Important changes in the brain transcriptome have been observed after acute SD (Cirelli and Tononi 2000; Mongrain et al. 2010), and recently, sleep loss was found to have a broad impact on the epigenetic landscape of the cerebral cortex, with DNA methylation and hydroxymethylation modifications highly enriched in genes involved in synaptic regulation (Massart et al. 2014) These data contribute to current hypotheses regarding the role for sleep in metabolism and energy regulation, synaptic plasticity, and neuroprotection.

Finally, a recent study found that astrocytes regulate response to SD, raising the possibility that glial signaling mediates antidepressant actions of TSD (Hines et al. 2013).

It could be then suggested that multiple extracellular signals, including 5-HT neurotransmission, could converge on pathways regulating synaptic plasticity and cell metabolism to cause rapid antidepressant effects as those observed after SD.

4 Conclusions and Future Perspectives

In conclusion, SD is a rapid, safe, and effective therapy for depression. In recent years, this technique has passed the experimental developmental phase and reached the status of affordable clinical intervention for everyday clinical therapy of depressed patients with an increasing literature regarding its safety and efficacy. The many neurobiological mechanisms involved in the response to this chronobiological intervention still remain obscure. Since SD therapy is an ideal experimental model to study mechanisms involved in rapid antidepressant actions, focusing on this chrobiological treatment and its mechanisms of action means increasing knowledge about the pathophysiology of mood disorders.

References

Adli M, Hollinde DL, Stamm T et al (2007) Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta −50T/C single nucleotide polymorphism. Biol Psychiatry 62:1295–1302

Adrien J (2002) Neurobiological bases for the relation between sleep and depression. Sleep Med Rev 6:341–351

Amin MM, Khalid R, Khan P (1980) Relationship between sleep deprivation and urinary MHPG levels. Int Pharmacopsychiatry 15:81–85

Asikainen M, Toppila J, Alanko L, Ward DJ, Stenberg D, Porkka-Heiskanen T (1997) Sleep deprivation increases brain serotonin turnover in the rat. NeuroReport 8:1577–1582

Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E (1998) The unipolar-bipolar dichotomy and the response to sleep deprivation. Psychiatry Res 79:43–50

Basheer R, Magner M, McCarley RW, Shiromani PJ (1998) REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. Brain Res Mol Brain Res 57:235–240

Baumgartner A, Riemann D, Berger M (1990) Neuroendocrinological investigations during sleep deprivation in depression. II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. Biol Psychiatry 28:569–587

Benedetti F, Barbini B, Campori E, Colombo C, Smeraldi E (1996) Dopamine agonist amineptine prevents the antidepressant effect of sleep deprivation. Psychiatry Res 65:179–184

Benedetti F, Barbini B, Lucca A, Campori E, Colombo C, Smeraldi E (1997) Sleep deprivation hastens the antidepressant action of fluoxetine. Eur Arch Psychiatry Clin Neurosci 247:100–103

Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E (1999a) Ongoing lithium treatment prevents relapse after total sleep deprivation. J Clin Psychopharmacol 19:240–245

Benedetti F, Serretti A, Colombo C et al (1999b) Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. Am J Psychiatry 156:1450–1452

Benedetti F, Zanardi R, Colombo C, Smeraldi E (1999c) Worsening of delusional depression after sleep deprivation: case reports. J Psychiatr Res 33:69–72

Benedetti F, Campori E, Barbini B, Fulgosi MC, Colombo C (2001) Dopaminergic augmentation of sleep deprivation effects in bipolar depression. Psychiatry Res 104:239–246

Benedetti F, Lucca A, Brambilla F, Colombo C, Smeraldi E (2002) Interleukine-6 serum levels correlate with response to antidepressant sleep deprivation and sleep phase advance. Prog Neuropsychopharmacol Biol Psychiatry 26:1167–1170

Benedetti F, Colombo C, Serretti A et al (2003a) Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. Biol Psychiatry 54:687–692

Benedetti F, Serretti A, Colombo C, Lilli R, Lorenzi C, Smeraldi E (2003b) Dopamine receptor D2 and D3 gene variants are not associated with the antidepressant effect of total sleep deprivation in bipolar depression. Psychiatry Res 118:241–247

Benedetti F, Bernasconi A, Lorenzi C et al (2004a) A single nucleotide polymorphism in glycogen synthase kinase 3-beta promoter gene influences onset of illness in patients affected by bipolar disorder. Neurosci Lett 355:37–40

Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E (2004b) A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. Neurosci Lett 368:123–126

Benedetti F, Barbini B, Fulgosi MC et al (2005a) Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. J Clin Psychiatry 66:1535–1540

Benedetti F, Serretti A, Pontiggia A et al (2005b) Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta −50 T/C SNP. Neurosci Lett 376:51–55

Benedetti F, Barbini B, Colombo C, Smeraldi E (2007a) Chronotherapeutics in a psychiatric ward. Sleep Med Rev 11:509–522

Benedetti F, Bernasconi A, Blasi V et al (2007b) Neural and genetic correlates of antidepressant response to sleep deprivation: a fMRI study of moral valence decision in bipolar depression. Arch Gen Psychiatry 64:179–187

Benedetti F, Dallaspezia S, Fulgosi MC, Barbini B, Colombo C, Smeraldi E (2007c) Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. Chronobiol Int 24:921–937

Benedetti F, Barbini B, Bernasconi A et al (2008a) Lithium overcomes the influence of 5-HTTLPR gene polymorphism on antidepressant response to sleep deprivation. J Clin Psychopharmacol 28:249–251

Benedetti F, Barbini B, Bernasconi A et al (2008b) Serotonin 5-HT2A receptor gene variants influence antidepressant response to repeated total sleep deprivation in bipolar depression. Prog Neuropsychopharmacol Biol Psychiatry 32:1863–1866

Benedetti F, Calabrese G, Bernasconi A et al (2009) Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. Psychiatry Res 173:238–242

Benedetti F, Barbini B, Bernasconi A et al (2010) Acute antidepressant response to sleep deprivation combined with light therapy is influenced by the catechol-O-methyltransferase Val (108/158)Met polymorphism. J Affect Disord 121:68–72

Benedetti F, Dallaspezia S, Lorenzi C et al (2011) Gene–gene interaction of glycogen synthase kinase 3-beta and serotonin transporter on human antidepressant response to sleep deprivation. J Affect Disord 136:514–519

Berger M, Vollmann J, Hohagen F et al (1997) Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. Am J Psychiatry 154:870–872

Bertolucci PH, Andrade LA, Lima JG, Carlini EA (1987) Total sleep deprivation and Parkinson disease. Arq Neuropsiquiatr 45:224–230

Borbely AA, Wirz-Justice A (1982) Sleep, sleep deprivation and depression. A hypothesis derived from a model of sleep regulation. Hum Neurobiol 1:205–210

Bunney BG, Bunney WE (2013) Mechanisms of rapid antidepressant effects of sleep deprivation therapy: clock genes and circadian rhythms. Biol Psychiatry 73:1164–1171

Bushey D, Tononi G, Cirelli C (2011) Sleep and synaptic homeostasis: structural evidence in Drosophila. Science 332:1576–1581

Canali P, Sferrazza Papa G, Casali AG et al (2014) Changes of cortical excitability as markers of antidepressant response in bipolar depression: preliminary data by combining TMS and EEG. Bipolar Disord

Cirelli C, Tononi G (2000) Gene expression in the brain across the sleep-waking cycle. Brain Res 885:303–321

Clark CP, Brown GG, Archibald SL et al (2006) Does amygdalar perfusion correlate with antidepressant response to partial sleep deprivation in major depression? Psychiatry Res 146:43–51

Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E (1999) Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res 86:267–270

Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E (2000) Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psychiatry Res 95:43–53

Davidson RJ, Irwin W, Anderle MJ, Kalin NH (2003) The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 160:64–75

Deboer T, Vansteensel MJ, Detari L, Meijer JH (2003) Sleep states alter activity of suprachiasmatic nucleus neurons. Nat Neurosci 6:1086–1090

Delva NJ, Woo M, Southmayd SE, Hawken ER (2001) Myocardial infarction during sleep deprivation in a patient with dextrocardia–a case report. Angiology 52:83–86

Demet EM, Chicz-Demet A, Fallon JH, Sokolski KN (1999) Sleep deprivation therapy in depressive illness and Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 23:753–784

Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A (1994) Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation–preliminary results. Biol Psychiatry 35:880–885

Ebert D, Albert R, Hammon G, Strasser B, May A, Merz A (1996) Eye-blink rates and depression. Is the antidepressant effect of sleep deprivation mediated by the dopamine system? Neuropsychopharmacology 15:332–339

Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ (2002) The neural basis of mood-congruent processing biases in depression. Arch Gen Psychiatry 59:597–604

Fahndrich E (1981) Effects of sleep deprivation on depressed patients of different nosological groups. Psychiatry Res 5:277–285

Frye MA, Helleman G, McElroy SL et al (2009) Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 166:164–172

Gardner JP, Fornal CA, Jacobs BL (1997) Effects of sleep deprivation on serotonergic neuronal activity in the dorsal raphe nucleus of the freely moving cat. Neuropsychopharmacology 17:72–81

Gerner RH, Post RM, Gillin JC, Bunney WE Jr (1979) Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. J Psychiatr Res 15:21–40

Gessa GL, Pani L, Fadda P, Fratta W (1995) Sleep deprivation in the rat: an animal model of mania. Eur Neuropsychopharmacol 5(Suppl):89–93

Giedke H, Schwarzler F (2002) Therapeutic use of sleep deprivation in depression. Sleep Med Rev 6:361–377

Giedke H, Wormstall H, Haffner HT (1990) Therapeutic sleep deprivation in depressives, restricted to the two nocturnal hours between 3:00 and 5:00. Prog Neuropsychopharmacol Biol Psychiatry 14:37–47

Giedke H, Geilenkirchen R, Hauser M (1992) The timing of partial sleep deprivation in depression. J Affect Disord 25:117–128

Grozinger M, Kogel P, Roschke J (2002) Effects of REM sleep awakenings and related wakening paradigms on the ultradian sleep cycle and the symptoms in depression. J Psychiatr Res 36:299–308

Grunze H, Erfurth A, Walden J (1999) Trimipramine fails to exert antimanic efficacy: a case of the discrepancy between in vitro rationale and clinical efficacy. Clin Neuropharmacol 22:298–300

Hamann S (2005) Blue genes: wiring the brain for depression. Nat Neurosci 8:701–703

Hanlon EC, Vyazovskiy VV, Faraguna U, Tononi G, Cirelli C (2011) Synaptic potentiation and sleep need: clues from molecular and electrophysiological studies. Curr Top Med Chem 11:2472–2482

Harvey AG (2008) Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry 165:820–829

Hefti K, Holst SC, Sovago J et al (2013) Increased metabotropic glutamate receptor subtype 5 availability in human brain after one night without sleep. Biol Psychiatry 73:161–168

Heils A, Mossner R, Lesch KP (1997) The human serotonin transporter gene polymorphism–basic research and clinical implications. J Neural Transm 104:1005–1014

Hines DJ, Schmitt LI, Hines RM, Moss SJ, Haydon PG (2013) Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. Transl Psychiatry 3: e212

Hipolide DC, Moreira KM, Barlow KB, Wilson AA, Nobrega JN, Tufik S (2005) Distinct effects of sleep deprivation on binding to norepinephrine and serotonin transporters in rat brain. Prog Neuropsychopharmacol Biol Psychiatry 29:297–303

Hogl B, Peralta C, Wetter TC, Gershanik O, Trenkwalder C (2001) Effect of sleep deprivation on motor performance in patients with Parkinson's disease. Mov Disord 16:616–621

Holsboer-Trachsler E, Hemmeter U, Hatzinger M, Seifritz E, Gerhard U, Hobi V (1994) Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment–neurobiological and psychometric assessment of course. J Psychiatr Res 28:381–399

Huber R, Maki H, Rosanova M et al (2013) Human cortical excitability increases with time awake. Cereb Cortex 23:332–338

Joffe RT, Swinson RP (1988) Total sleep deprivation in patients with obsessive-compulsive disorder. Acta Psychiatr Scand 77:483–487

Kasper S, Moises HW, Beckmann H (1983) Dexamethasone suppression test combined with total sleep deprivation in depressed patients. Psychiatr Clin (Basel) 16:17–25

Kasper S, Sack DA, Wehr TA, Kick H, Voll G, Vieira A (1988) Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in patients with major depression. Biol Psychiatry 24:631–641

Kavcic P, Rojc B, Dolenc-Groselj L, Claustrat B, Fujs K, Poljak M (2011) The impact of sleep deprivation and nighttime light exposure on clock gene expression in humans. Croat Med J 52:594–603

Kuhs H, Tolle R (1991) Sleep deprivation therapy. Biol Psychiatry 29:1129–1148

Kwok JB, Hallupp M, Loy CT et al (2005) GSK3B polymorphisms alter transcription and splicing in Parkinson's disease. Ann Neurol 58:829–839

Leibenluft E, Wehr TA (1992) Is sleep deprivation useful in the treatment of depression? Am J Psychiatry 149:159–168

Lim MM, Xu J, Holtzman DM, Mach RH (2011) Sleep deprivation differentially affects dopamine receptor subtypes in mouse striatum. NeuroReport 22:489–493

Lopez-Rodriguez F, Wilson CL, Maidment NT, Poland RE, Engel J (2003) Total sleep deprivation increases extracellular serotonin in the rat hippocampus. Neuroscience 121:523–530

Manji HK, Quiroz JA, Payne JL et al (2003) The underlying neurobiology of bipolar disorder. World Psychiatry 2:136–146

Martiny K, Refsgaard E, Lund V et al (2013) The day-to-day acute effect of wake therapy in patients with major depression using the HAM-D6 as primary outcome measure: results from a randomised controlled trial. PLoS ONE 8:e67264

Massart R, Freyburger M, Suderman M et al (2014) The genome-wide landscape of DNA methylation and hydroxymethylation in response to sleep deprivation impacts on synaptic plasticity genes. Transl Psychiatry 4:e347

Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G (2005) Breakdown of cortical effective connectivity during sleep. Science 309:2228–2232

Matussek N, Romisch P, Ackenheil M (1977) MHPG excretion during sleep deprivation in endogenous depression. Neuropsychobiology 3:23–29

Mogilnicka E (1981) REM sleep deprivation changes behavioral response to catecholaminergic and serotonergic receptor activation in rats. Pharmacol Biochem Behav 15:149–151

Mongrain V, Hernandez SA, Pradervand S et al (2010) Separating the contribution of glucocorticoids and wakefulness to the molecular and electrophysiological correlates of sleep homeostasis. Sleep 33:1147–1157

Mongrain V, La Spada F, Curie T, Franken P (2011) Sleep loss reduces the DNA-binding of BMAL1, CLOCK, and NPAS2 to specific clock genes in the mouse cerebral cortex. PLoS ONE 6:e26622

Muller HU, Riemann D, Berger M, Muller WE (1993) The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. Acta Psychiatr Scand 88:16–20

Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S (1996) Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. Biol Psychiatry 39:16–21

Nissen C, Feige B, Konig A, Voderholzer U, Berger M, Riemann D (2001) Delta sleep ratio as a predictor of sleep deprivation response in major depression. J Psychiatr Res 35:155–163

Parry BL, Curran ML, Stuenkel CA et al (2000) Can critically timed sleep deprivation be useful in pregnancy and postpartum depressions? J Affect Disord 60:201–212

Payne JL, Quiroz JA, Zarate CA Jr, Manji HK (2002) Timing is everything: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation? Biol Psychiatry 52:921–926
Peet M (1994) Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 164:549–550
Pezawas L, Meyer-Lindenberg A, Drabant EM et al (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8:828–834
Reinink E, Bouhuys N, Wirz-Justice A, van den Hoofdakker R (1990) Prediction of the antidepressant response to total sleep deprivation by diurnal variation of mood. Psychiatry Res 32:113–124
Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306:443–447
Riemann D, Hohagen F, Konig A et al (1996) Advanced vs. normal sleep timing: effects on depressed mood after response to sleep deprivation in patients with a major depressive disorder. J Affect Disord 37:121–128
Riemann D, Konig A, Hohagen F et al (1999) How to preserve the antidepressive effect of sleep deprivation: a comparison of sleep phase advance and sleep phase delay. Eur Arch Psychiatry Clin Neurosci 249:231–237
Robbins TW (2005) Controlling stress: how the brain protects itself from depression. Nat Neurosci 8:261–262
Roy-Byrne PP, Uhde TW (1984) Post RM antidepressant effect of one night's sleep deprivation: clinical and theoretical implications. In: Post RM, Ballenger JC (eds) Neurobiology of mood disorders. William & Wilkins, Baltimore, pp 817–835
Roy-Byrne PP, Uhde TW, Post RM (1986) Effects of one night's sleep deprivation on mood and behavior in panic disorder. Patients with panic disorder compared with depressed patients and normal controls. Arch Gen Psychiatry 43:895–899
Ruhe HG, Ooteman W, Booij J et al (2009) Serotonin transporter gene promoter polymorphisms modify the association between paroxetine serotonin transporter occupancy and clinical response in major depressive disorder. Pharmacogenet Genomics 19:67–76
Salomon RM, Delgado PL, Licinio J, Krystal JH, Heninger GR, Charney DS (1994) Effects of sleep deprivation on serotonin function in depression. Biol Psychiatry 36:840–846
Santos R, Carlini EA (1983) Serotonin receptor activation in rats previously deprived of REM sleep. Pharmacol Biochem Behav 18:501–507
Savelyev SA, Rantamaki T, Rytkonen KM, Castren E, Porkka-Heiskanen T (2012) Sleep homeostasis and depression: studies with the rat clomipramine model of depression. Neuroscience 212:149–158
Schulte W (1971) Zum Priblem der provokation und kupierung von Melancholischen Phasen. Schweizer Arch Neurol Neurochem Psychiatr 109:427–435
Selvi Y, Gulec M, Agargun MY, Besiroglu L (2007) Mood changes after sleep deprivation in morningness-eveningness chronotypes in healthy individuals. J Sleep Res 16:241–244
Serretti A, Benedetti F, Colombo C, Lilli R, Lorenzi C, Smeraldi E (1999) Dopamine receptor D4 is not associated with antidepressant activity of sleep deprivation. Psychiatry Res 89:107–114
Serretti A, Benedetti F, Zanardi R, Smeraldi E (2005) The influence of Serotonin Transporter Promoter Polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments. Prog Neuropsychopharmacol Biol Psychiatry 29 (6):1074–1084
Siegel JM, Rogawski MA (1988) A function for REM sleep: regulation of noradrenergic receptor sensitivity. Brain Res 472:213–233
Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C (1999) Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression—a placebo-controlled trial. Neuropsychopharmacology 20:380–385
Suh SY, Kim JW, Choi CU et al (2007) Spontaneous coronary dissection associated with sleep deprivation presenting with acute myocardial infarction. Int J Cardiol 115:e78–e79

Sulzer D, Edwards RH (2005) Antidepressants and the monoamine masquerade. Neuron 46:1–2
Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62:143–150
Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
Tufik S, Lindsey CJ, Carlini EA (1978) Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? Pharmacology 16:98–105
van den Burg W, Bouhuys AL, van den Hoofdakker RH, Beersma DG (1990) Sleep deprivation in bright and dim light: antidepressant effects on major depressive disorder. J Affect Disord 19:109–117
Vogel GW, Thurmond A, Gibbons P, Sloan K, Walker M (1975) REM sleep reduction effects on depression syndromes. Arch Gen Psychiatry 32:765–777
Volkow ND, Wang GJ, Telang F et al (2008) Sleep deprivation decreases binding of [11C] raclopride to dopamine D2/D3 receptors in the human brain. J Neurosci 28:8454–8461
Volkow ND, Tomasi D, Wang GJ et al (2012) Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. J Neurosci 32:6711–6717
Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11:200–208
Wehr TA, Rosenthal NE, Sack DA, Gillin JC (1985) Antidepressant effects of sleep deprivation in bright and dim light. Acta Psychiatr Scand 72:161–165
Wirz-Justice A, Van den Hoofdakker RH (1999) Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry 46:445–453
Wirz-Justice A, Tobler I, Kafka MS et al (1981) Sleep deprivation: effects on circadian rhythms of rat brain neurotransmitter receptors. Psychiatry Res 5:67–76
Wirz-Justice A, Benedetti F, Berger M et al (2005) Chronotherapeutics (light and wake therapy) in affective disorders. Psychol Med 35:939–944
Wirz-Justice A, Benedetti F, Terman M (2009) Chronotherapeutics for affective disorders. A clinician's manual for light and wake therapy. Karger, Basel
Wu J, Buchsbaum MS, Gillin JC et al (1999) Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry 156:1149–1158

Pharmacological Treatment of Sleep Disorders and Its Relationship with Neuroplasticity

Vivien C. Abad and Christian Guilleminault

Abstract Sleep and wakefulness are regulated by complex brain circuits located in the brain stem, thalamus, subthalamus, hypothalamus, basal forebrain, and cerebral cortex. Wakefulness and NREM and REM sleep are modulated by the interactions between neurotransmitters that promote arousal and neurotransmitters that promote sleep. Various lines of evidence suggest that sleep disorders may negatively affect neuronal plasticity and cognitive function. Pharmacological treatments may alleviate these effects but may also have adverse side effects by themselves. This chapter discusses the relationship between sleep disorders, pharmacological treatments, and brain plasticity, including the treatment of insomnia, hypersomnias such as narcolepsy, restless legs syndrome (RLS), obstructive sleep apnea (OSA), and parasomnias.

Keywords Pharmacology · Sleep · Wake · Neuroplasticity · Neurotransmitters · Treatment · Insomnia · Narcolepsy · Restless legs · Obstructive sleep apnea · Parasomnias

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1 Sleep, Sleep Disorders, and Neuroplasticity

Sleep and wakefulness are states of being that are regulated by complex brain circuitry, located primarily in the brain stem, thalamus, subthalamus, hypothalamus, basal forebrain, and cerebral cortex. Sleep promotes neuronal and synaptic plasticity and is functionally linked to learning, memory, and emotion (Poe et al. 2010; Walker and Stickgold 2004; Walker 2009). Sleep prepares the hippocampus for encoding new experiences and modulates the post-encoding consolidation of both non-specific and specific recently encoded experiences, based on explicit as well as saliency cues gathered (Saletin and Walker 2012; Walker 2010; Stickgold and Walker 2013). These encoding and consolidation operations may occur during specific non-rapid eye movement (NREM) sleep and/or rapid eye movement (REM) sleep physiological oscillations to achieve optimal network outcome (Saletin and Walker 2012). During NREM Stage 2 sleep spindles, the cessation and subsequent bursting of noradrenergic cells and reactivation of hippocampal and cortical targets increase synaptic plasticity and bidirectional plasticity in the neocortex (Poe et al. 2010; Wang et al. 2011). Orderly neuronal reactivation events that occur in phase with slow-wave delta activity together with high protein synthesis levels facilitate the conversion of early long-term potentiation (LTP) to long-lasting LTP (Poe et al. 2010). Delta sleep does not activate immediate early genes associated with de novo LTP, but coincidentally activated cortical circuits may be reduced in strength (Poe et al. 2010). During REM sleep, bidirectional plasticity, LTP, and depotentiation are present together with PGO waves, theta synchrony, increased acetylcholine, reduced monoamine levels, and increased transcription of plasticity-related genes within the neurons (Poe et al. 2010; Wang et al. 2011). Sleep disorders may negatively affect neuronal plasticity with consequent alteration in brain function, particularly when these disorders are associated with sleep loss and sleep instability (Havekes et al. 2012; Shepherd 2012; Gao 2012; Hefti et al. 2013).

2 Physiology and Pharmacology of Normal Sleep–Wake States

Sleep/wake states may represent a flip-flop switch between sleep-promoting systems and arousal-promoting systems in the brain (Saper et al. 2005; Espana and Scammell 2004). The wakefulness and arousal network emanates from pontine and midbrain reticular nuclei, with fibers ascending through dorsal and ventral pathways; they are mainly composed of glutamatergic neurons, which are modulated by cholinergic and monoaminergic tone. The dorsal pathway projects to the thalamus from the cholinergic pedunculopontine and laterodorsal tegmental nuclei. Key relay structures between the midbrain reticular formation and the cortex are the thalamus, posterior hypothalamus, and basal forebrain. Cholinergic thalamocortical projections induce electroencephalogram (EEG) activation, while cholinergic projections from the basal forebrain maintain arousal. Hypocretin fibers from the perifornical lateral hypothalamus activate monoaminergic neurons, promote wakefulness, and stabilize boundaries between wake and REM sleep (Boutrel and Koob 2004). Histaminergic neurons modulate behavioral and cortical arousal. Fibers from histaminergic neurons in the tuberomammillary nucleus of the posterior hypothalamus ascend and project to the cortex, basal forebrain, and limbic structures, while descending fibers project to brain stem monoaminergic and cholinergic centers. Other substances that may lead to cortical activation include vasoactive intestinal peptide, corticotropin-releasing factor, thyrotropin-releasing factor, thyrotropin-stimulating hormone, epinephrine, and adrenocorticotropic hormone.

Adenosine receptors activate sleep-regulatory neurons in the ventrolateral preoptic and median preoptic area, inducing gamma-amino butyric acid (GABA) and galaninergic inhibition of ascending arousal (Boutrel and Koob 2004; Buysse 2011). The homeostatic and circadian systems regulate the timing and level of activity of the lateral hypothalamus and preoptic nuclei, in order to maintain a dynamic equilibrium between them, thereby sustaining stable sleep–wake states. The ventrolateral preoptic neurons are reciprocally inhibited by inputs from histaminergic, noradrenergic, serotonergic, and cholinergic systems (Gallopin et al. 2000). Synchronization of thalamocortical circuits results in sleep spindles or slow-wave activity. Sleep spindles close the gate to sensory input during sleep. Sleep oscillates between NREM and REM sleep, with reciprocal monoaminergic and cholinergic interactions. Descending inputs from cortical-diencephalic cognitive and affective centers also modulate sleep–wake balance and are also modulated by ascending inputs from the arousal system.

Sleep occurs when the hypothalamic switch shuts off the arousal system (Saper et al. 2005; Espana and Scammell 2004). Figure 1 depicts the key components of the ascending arousal system, while Fig. 2 shows the ventrolateral preoptic projections to the ascending arousal system (Saper et al. 2005). The flip-flop model for REM sleep posits a mutual inhibition between the REM-on GABAergic neurons in the sublaterodorsal tegmental nuclei in rats and the REM-off GABAergic neurons located in the ventrolateral periaqueductal gray matter and lateral pontine

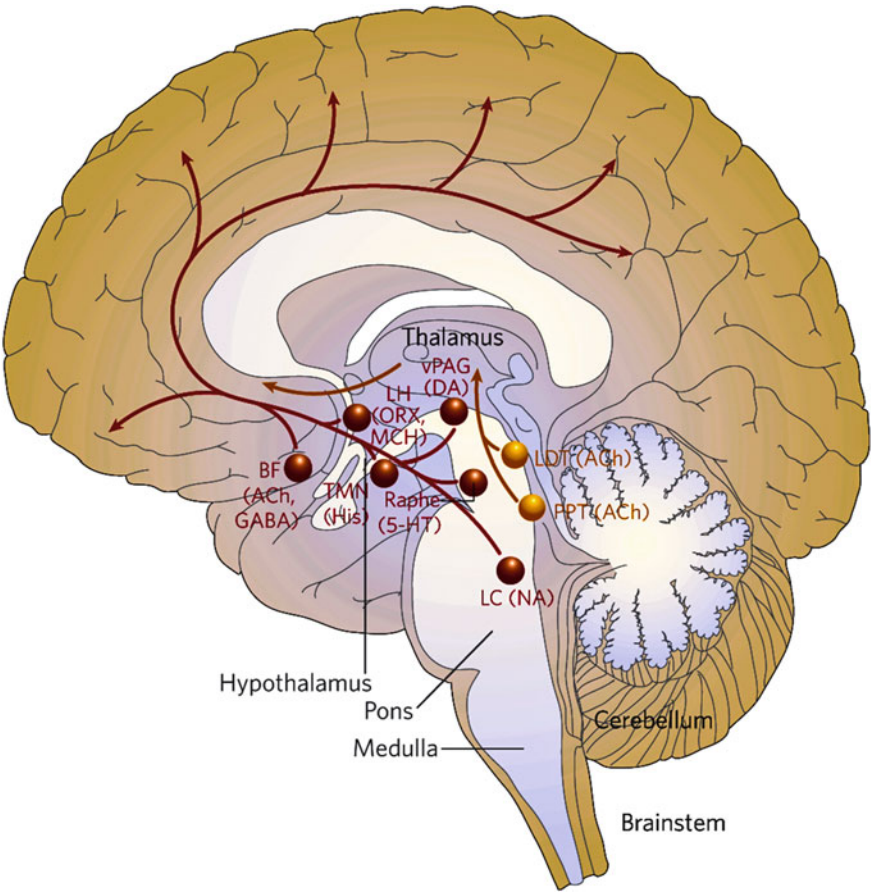

Fig. 1 Key components of the ascending arousal system. Cholinergic (*ACh*) inputs from the pedunculopontine (*PPT*) and laterodorsal tegmental (*LDT*) nuclei to the relay and reticular nuclei of the thalamus (*yellow* pathway) facilitate thalamocortical transmission. Monoaminergic cell groups, including the tuberomammillary nucleus (*TMN*) containing histamine (*His*), the A10 cell groups in ventral periaqueductal gray (*vPAG*) nucleus containing dopamine (*DA*), the median raphe nuclei containing serotonin (*5-HT*), and the locus coeruleus (*LC*) containing noradrenaline (*NE*) activate the cerebral cortex through a second pathway (*red*) to facilitate processing of inputs from the thalamus. This ventral pathway also receives contributions from peptidergic neurons in the lateral hypothalamus (*LHA*) containing orexin or melanin-concentrating hormone (*MCH*) and from basal forebrain (*BF*) neurons that contain gamma-aminobutyric acid (*GABA*) or ACh. Reprinted by permission from Macmillan Publisher Ltd: [Nature Publishing Group] (Saper et al. 2005), copyright (2005)

tegmentum. There are 2 populations of REM-on glutamatergic neurons: The first group projects to the basal forebrain and medial septum and regulates the EEG component of REM sleep, while the second group projects to the ventrolateral medulla and spinal cord and regulates REM-related atonia (Fuller et al. 2007).

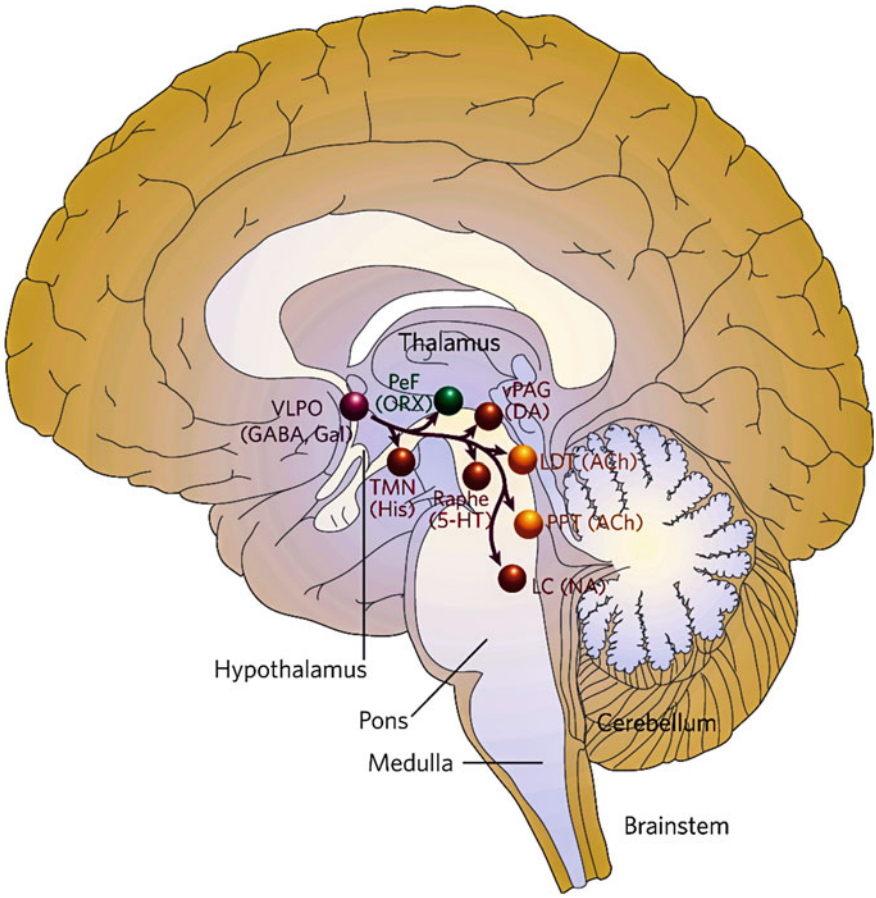

Fig. 2 Key projections of the ventrolateral preoptic nucleus (*VLPO*) to the main components of the ascending arousal system. The VLPO projects to the monoaminergic cell groups (*red*), such as the A10 cell groups in ventral periaqueductal gray (*vPAG*) nucleus containing dopamine (*DA*), the raphe cell groups, the tuberomammillary nucleus (*TMN*), and the locus coeruleus (*LC*). The VLPO also innervates neurons located in the lateral hypothalamus (*LHA*; *green*), including the perifornical (*PeF*) orexin (*ORX*) neurons, and interneurons in the cholinergic (*ACh*) cell groups (*yellow*), the pedunculopontine (*PPT*), and laterodorsal tegmental nuclei (*LDT*). *5-HT* serotonin, *GABA* gamma-aminobutyric acid, *gal* galanin, *NA* noradrenaline, and *His* histamine. Reprinted by permission from Macmillan Publisher Ltd: [Nature Publishing Group] (Saper et al. 2005), copyright (2005)

3 Insomnia and Its Pharmacological Treatments

Thirty to fifty percent of adults complain of insomnia, which may be transient or episodic, short-term, or chronic in duration. Chronic insomnia impairs mood, motor performance, and cognition. Insomnia also is a common problem in children. The estimated prevalence of pediatric insomnia including bedtime refusal and night

awakenings is 10–30 % among normal infants, toddlers, and preschoolers; in children with neurodevelopmental and psychiatric disorders, the prevalence rises to 50–75 % (Mindell et al. 2006). Chronic insomnia occurs in 4–7 % of children (Zhang et al. 2011).

3.1 Insomnia, Brain Morphology, and Cognitive Function

Chronic insomnia affects neuroplasticity and cognitive function. Functional magnetic resonance imaging (fMRI) scanning while performing a category and a letter fluency task demonstrated hypoactivation of the medial and inferior prefrontal cortical areas in chronic insomnia patients compared to normal controls, which recovered after 6 weeks of non-pharmacological sleep therapy (Altena et al. 2008). Chronic primary insomnia patients had reduced gray matter volume in the left orbitofrontal cortex, which strongly correlated with insomnia severity; gray matter volume in the anterior and posterior precuneus was also reduced (Altena et al. 2010). A transcranial magnetic stimulation (TMS) study in chronic insomnia patients found relatively reduced intracortical facilitation, but globally increased absolute excitability to both suprathreshold single- and paired-pulse stimulation, which persisted even after sleep therapy (Van der Werf et al. 2010). These findings favor the "activating" profile in chronic insomnia (Lanza et al. 2014) and could also suggest an optimal therapeutic window to start therapy before structural changes occur (Van der Werf et al. 2010). Further research is needed to elucidate this.

3.2 Insomnia Treatment

The primary treatment goals for insomnia are to improve sleep quality and quantity and to eradicate related daytime impairments (Schutte-Rodin et al. 2008). Psychological and behavioral interventions are recommended as initial interventions; they may also supplement hypnotic prescriptions (Schutte-Rodin et al. 2008).

Most hypnotic agents are approved for short-term use only. Some patients with severe or refractory insomnia or chronic comorbid illness use chronic hypnotic medications either nightly or intermittently, as needed. Adequate cognitive behavioral treatment (CBT) should be tried in these patients. Combined CBT and pharmacotherapy does not show any consistent advantage or disadvantage compared to CBT alone in patients with chronic insomnia.

Hypnotics presumably act either by blocking neurotransmitters that promote arousal or facilitating the neurotransmitters that drive sleep. Hypnotic agents (benzodiazepines and non-benzodiazepines) facilitate GABA receptors. Most of the agents that block wake promotion are histamine antagonists (usually H_1 receptor antagonists, such as diphenhydramine, low-dose doxepin, low-dose mirtazapine, novel selective H_1 receptor antagonists, and 5 HT_{2A} antagonists); some of these

agents may also exert antimuscarinic actions and/or anti-adrenergic effects. Orexin receptor antagonists also produce sleepiness with much greater and longer effects in man than any previous compound.

In children less than 5 years old, the mainstay of treatment remains empirically supported behavioral interventions (graduated extinction, parent education, delayed bedtime with removal from bed/positive bedtime routines) (Morgenthaler et al. 2006). Optimizing the sleep environment, sleep–wake scheduling, sleep practices, and addressing physiological factors (such as caffeine intake) are important adjunctive measures. The use of medications to treat pediatric insomnia should be approached carefully. Many forms of neuroplasticity peak during early developmental stages and might be affected by pharmacologic agents; injury to the developing brain can alter neuronal activity, modify synaptic mechanisms, and interfere with normal development and plasticity (Cramer et al. 2011). Pharmacological treatment is merely adjunctive and should follow general guidelines: (1) use the lowest effective dose and the shortest duration possible (usually <1 month), (2) avoid early evening dosing (due to circadian alerting), and (3) adjust dose based on pediatric metabolic profile of the drug. Comorbid primary sleep disorders should be addressed, and medication side effects should be monitored (Owens and Mindell 2011).

3.2.1 Benzodiazepine Receptor Agonists

GABA is the predominant inhibitory neurotransmitter in the central nervous system. The $GABA_A$-benzodiazepine receptor complex is a ligand-gated ion channel complex, which consists of 3 moieties: a $GABA_A$ recognition site, a benzodiazepine recognition site, and a chloride ionophore. $GABA_A$ has at least 5 glycoprotein subunits, each of which include multiple isoforms (α1-6, β1-3, γ1-3, δ1, ε1, θ1, and ρ1-3) (Vinkers and Olivier 2012). The most common isoforms noted are Type I (α1β2γ2) and Type II (α3β2γ2) configurations.

GABA receptors mediate two forms of inhibition: Phasic inhibition is generated by postsynaptic $GABA_A$ receptors, while tonic inhibition is primarily mediated by extrasynaptic $GABA_A$ receptors that contain either the δ subunit or the α sub-unit (Whissell et al. 2013). GABAergic synapses are also capable of activity-dependent long-term plasticity and LTP/long-term depression and spike-timing dependent plasticity (Maffei 2011).

Various hypnotic medications target $GABA_A$ receptors. Increased $GABA_A$-mediated inhibition in the thalamus and neocortex promotes slow oscillations and EEG spindles.

Classic benzodiazepines have a high affinity for multiple receptor subunits and bind to both Type I and Type II receptors, while non-benzodiazepine hypnotics, such as zolpidem and zaleplon, have more selective affinity for Type I receptors. Zolpidem's affinity is highest for the α1βχγ2, while eszopiclone's affinity is for α3 ≫ α1. Gaboxadol has a high affinity for extrasynaptic $GABA_A$ receptors δ subunit.

Absorption of benzodiazepine receptor agonists permits rapid sleep onset; the elimination half-life and dose determine the duration of somnogenic action and residual sedation (if any). Most benzodiazepines used as hypnotics (except for temazepam) have maximal absorption usually within 1–1.5 h; many are lipophilic and elimination half-lives vary.

The "Z" drugs (zolpidem, zaleplon, zopiclone, eszopiclone) have no significant effect on sleep-disordered breathing. The incidence of misuse of these agents is lower, although cases of chronic abuse, tolerance, misuse, and withdrawal symptoms of zolpidem have been reported (Victorri-Vigneau et al. 2007).

Adverse effects should be recognized. Cognitive impairment and impaired psychomotor performance can occur at peak levels, while long medication half-life can result in daytime sedation. Anterograde amnesia may occur with triazolam and the non-benzodiazepines, particularly when combined with alcohol. Confusional arousals or sleepwalking episodes or sleep eating have been reported. Nighttime falls in the elderly are increased. Other side effects include tolerance, abuse, and withdrawal. Rebound insomnia (the occurrence of insomnia symptoms worse than baseline) can occur for 1–2 days after abrupt withdrawal following prolonged benzodiazepine use.

Anterograde amnesia and impaired cognitive function may be related to changes in neuroplasticity with hypnotic use. GABAergic inhibition modulates excitatory synaptic plasticity, while GABA receptor blockers promote LTP of glutamatergic transmission in the hippocampus and neocortex (Nitsche et al. 2012). During high-frequency synaptic transmission, GABAergic inhibition is released by auto-inhibition of GABAergic terminals via $GABA_B$ receptors. This then allows postsynaptic depolarization to activate N-methyl-D-aspartate receptors and induce LTP (Davies et al. 1991). In rats, lorazepam (a long-acting benzodiazepine) impaired both recognition memory and synaptic plastic processes (long-term depression and LTP) in the peri-rhinal cortex (Wan et al. 2004). In cats, zolpidem significantly reduced cortical plasticity by $\sim 50\,\%$; this effect was not due to abnormal sleep architecture (Seibt et al. 2008). Also, in cats, triazolam (a short-acting benzodiazepine) impaired sleep architecture and resulted in EEG abnormalities, but did not affect cortical plasticity (Seibt et al. 2008). In mice, acute administration of $\delta GABA_A$ receptor agonist impaired memory behaviors and inhibited synaptic plasticity (Whissell et al. 2013).

The long-term effects of chronic use of benzodiazepines and benzodiazepine receptor agonists on neuroplasticity and cognitive function are of concern (Barker et al. 2004, 2005). Results from a meta-analysis of 13 studies that utilized psychological tests indicated that chronic insomnia patients on long-term benzodiazepine treatment had worse cognition compared to control subjects; impairment in certain domains persisted even after discontinuation of hypnotic use (Barker et al. 2004). Test performance in all 12 cognitive domains examined was worse in the benzodiazepine group, with effect sizes ranging in magnitude from -1.30 to -0.42 (Barker et al. 2004). Even after >6 months of withdrawal from long-term benzodiazepine use (mean use 108 months), verbal memory, motor control/performance, and nonverbal memory were impaired, while visuospatial skills and attention/concentration were not (Barker et al. 2004). Majority of the patients in the studies

included in the above meta-analyses had utilized benzodiazepines to control anxiety/depression. Of the 7 studies that used a control group, 1 study used a healthy control group and an anxious control group, while 6 recruited control subjects from the general population with no history of anxiety (Barker et al. 2004). A caveat, therefore, in interpreting these results is that reduced performance after benzodiazepine withdrawal could be due to recurrence of pre-morbid symptomatology. Similar findings were reported in a study of 89 older adults (mean age ≥55 years) on chronic benzodiazepine therapy and who were studied at baseline and after withdrawal from benzodiazepines/benzodiazepine receptor agonists for a period up to 6 months. Prolonged impairment of attentional and psychomotor cognition function was noted; again, findings persisted for at least 6 months following drug withdrawal (Puustinen et al. 2014).

3.2.2 Antihistamines and Sedating Antidepressants

Histamine H1 receptors are present in the cortex, hippocampus, amygdala, hypothalamus, striatum, and cerebellum, while H2 receptors are located in the basal ganglia, amygdala, hippocampus, and cortex. The H3 receptors are found in the histaminergic neurons. Histamine receptors (H_1 and H_2) are postsynaptic, while H_3 receptors are presynaptic. H_1 receptor binding promotes wakefulness, while H_2 receptor antagonists promote slow-wave sleep (Stahl 2008). H_3 receptors are both autoreceptors and heteroreceptors: Binding at these sites inhibits histamine and norepinephrine release.

Activation of H1 or H2 receptors leads to downstream signaling cascades that can mediate functional and structural changes in synapses. H3 receptors might affect synaptic plasticity in the hippocampus and striatum by reducing the release of several neurotransmitters including glutamate. H3 receptor activation hinders synaptic transmission and reduces paired-pulse facilitation in the dentate gyrus (Kohler et al. 2011). Infusion of H1 and H2 receptor antagonists and H3 receptor agonist in the hippocampus of rats blocked long-term memory retention, suggesting that object recognition memory is modulated through H1, H2, and H3 receptors (da Silveira et al. 2013). An experiment in mice suggested that histamine-induced emotional memory consolidation is mediated by H1 but not H2 receptors (Gianlorenco et al. 2012).

Diphenhydramine blocks H_1 receptors and is FDA-approved for short-term use to treat occasional sleeplessness. Doses in adults range from 50–100 mg at bedtime. Pediatric dosing ranges from 1 mg/kg up to 50 mg per day. Absorption is rapid, peak sedative effect occurs at 1–3 h after dose, and sedation lasts 4–7 h. Side effects include daytime drowsiness, cholinergic effects, and paradoxical excitation. Adult patients with rhinitis, taking 50 mg of diphenhydramine were more sleepy, less vigilant, and performed worse across all cognitive domains in a comprehensive battery of automated neuropsychological tests compared to patients on desloratadine 5 mg or placebo (Wilken et al. 2003).

Low-dose doxepin (Silenor) is FDA-approved for the treatment of sleep maintenance insomnia. Compared to placebo, low-dose doxepin (1, 3, 6 mg) significantly improved wake after sleep onset (WASO), total sleep time (TST), and overall sleep efficiency; at 6 mg, it also significantly reduced subjective latency to sleep onset (Roth et al. 2007). Doxepin is a tricyclic drug that blocks histaminergic, cholinergic, and alpha-1 noradrenergic receptors and also inhibits reuptake of norepinephrine and serotonin. Ultra-low-dose doxepin is a selective H1 antagonist, as it has high affinity for H1 receptors but little effect on serotonergic or adrenergic receptors. Dosage is 6 mg for adults and 3 mg for the elderly. The most common side effects are somnolence, headache, nausea, and occasionally upper respiratory tract infection. The effects of doxepin use on plasticity are discussed in the section concerning off-label insomnia drugs with the other antidepressants.

3.2.3 Melatonin Receptor Agonists

Over the counter melatonin formulations vary in purity and strength. Melatonin taken 30–120 min before sleep shortens latency to persistent sleep (LPS) but is not effective in maintaining sleep (Olde Rikkert and Rigaud 2001). Half-life in the immediate release formulations is 30–50 min versus 2 h in the sustained release formulations. It is used to treat acute or chronic circadian rhythm disturbances in normal or blind children. Reported doses for melatonin range from 1 mg in infants, 2.5–3 mg in older children, and 5 mg in adolescents: Doses ranging from 0.5 to 10 mg have been used in children with special needs (Owens 2009). In adults with delayed sleep phase syndrome, 0.5 mg taken 5–7 h before sleep onset may shorten sleep-onset delays. Phase shifting effects of melatonin are attributed to melatonin receptors MT_1 and MT_2, which are highly prevalent in the retina and suprachiasmatic nucleus. Melatonin impairs performance in some neurocognitive tasks such as reaction time, tracking, vigilance, and spatial memory.

Ramelteon, a synthetic melatonin receptor agonist (MT_1 and MT_2 receptors), is FDA-approved for the treatment of sleep-onset insomnia in adults, and for sleep maintenance insomnia only by the European Community Agency, but is not approved for use in children and adolescents. The recommended nightly dose for treatment of adults with insomnia is 8 mg. Safety data from animal models suggest that ramelteon has a low risk of cognitive impairment and physiological dependence (France et al. 2006; Rajaratnam et al. 2009a, b). Efficacy in pediatric autistic cases has been reported (Owens and Mindell 2011). Peak absorption is within 0.75–1 h, and half-life ranges from 0.8–2.5 h (Karim et al. 2006). Main side effects include somnolence, dizziness, and fatigue. Ramelteon does not produce tolerance, withdrawal, rebound insomnia, cognitive impairment, or psychomotor retardation. It can be used in patients with substance abuse histories as well as in patients with mild to moderate pulmonary disease. It is metabolized by cytochrome (CYP)$1A_2$ and should not be used with fluvoxamine. It does not significantly affect memory,

digit symbol substitution, dual attention, auditory tracking, letter cancellation, or driving performance (Mets et al. 2011).

Non-24 h sleep–wake disorder (hypernyctohemeral syndrome) is a circadian rhythm sleep disorder that affects individuals who lack the capacity to synchronize their circadian clock with the external environment. Total blindness, major psychiatric disorders, and structural lesions of the hypothalamus are comorbid conditions. Affected individuals present with difficulty in initiating sleep and progressively delayed sleep onset and offset. Tasimelteon is the only drug that is currently approved by the FDA to treat non-24-h sleep–wake disorder; the recommended dose is 20 mg at night before bedtime, taken without food. Tasimelteon is a MT_1/MT_2 agonist with a higher affinity for the MT-2 receptor; its elimination half-life is 1.3–3.7 h, and peak concentration is at 2 h; it is metabolized mainly by CYP1A2 and CYP3A4 enzymes (Bonacci et al. 2014). Tasimelteon (10, 20, 50, 100 mg) reduced sleep latency and increased sleep efficiency in healthy adults and in adults with transient insomnia; WASO significantly improved at higher doses (20, 50 mg). Phase shifting was dose dependent. Adverse events included somnolence and headache, but were similar to placebo (Rajaratnam et al. 2009a, b). Twenty milligram of tasimelteon at night entrained the master clock, reduced daytime sleepiness, increased nighttime sleep, and optimized sleep timing in 84 blind participants with non-24 h sleep disorder (Johnsa and Neville 2014). Tasimelteon was also better than placebo in maintaining entrainment and continuing to improve sleep and wake parameters (Johnsa and Neville 2014).

Agomelatine, a melatonergic MT_1/MT_2 agonist and an antagonist for $5\text{-}HT_{2B}$ and $5\text{-}HT_{2C}$, improves insomnia associated with depression in manic-depressive (MD) disorders and major depressive disorders (MDD). By blocking $5\text{-}HT_{2C}$ receptors, agomelatine induces release of both NE and DA. At a dose of 25 mg/day, agomelatine improved sleep efficiency, slow-wave sleep, and distribution of delta activity throughout the night, but did not affect REM sleep latency or amount of REM sleep (Quera-Salva et al. 2010). Agomelatine has been approved in Europe for several years, but development for the US market was discontinued after the results of Phase III trials. Agomelatine appears similar in efficacy to other antidepressants but requires liver monitoring because of 1.3 % incidence of elevated liver enzymes and 6 cases of non-fatal toxic hepatitis had been reported (Taylor 2014).

Importantly, there is evidence from experimental studies in animals indicating that melatonin and melatonin analogs may affect neuronal plasticity. In rats, subjected to experimental stroke or glutamate excitotoxicity, melatonin administration improved neuroplasticity in cultured neurons by significantly upregulating growth associated protein-43, NMDAR postsynaptic density-95, and matrix metalloproteinase-9 protein (Juan et al. 2013). Also, chronic agomelatine administration enhanced hippocampal cell proliferation and survival in stressed rats but not in control rats (Dagyte et al. 2010). On the other hand, in other studies, ramelteon did not affect NREM or REM sleep, did not affect ocular dominance plasticity, and did not affect learning or memory (Seibt et al. 2008; Hirai et al. 2005).

3.2.4 Off-label Insomnia Drugs

Of the four most commonly prescribed hypnotic agents, three are antidepressants that are prescribed off-label: trazodone, amitriptyline, and mirtazapine (Walsh 2004). Tricylic antidepressants (TCAs) such as amitriptyline and doxepin (1) inhibit serotonin (5 HT) and norepinephrine (NE) reuptake transporters; (2) desensitize presynaptic 5 HT_{1A} autoreceptors, sensitize postsynaptic 5 HT_{1A} receptors, and both downregulate and antagonize postsynaptic 5 HT_2 receptors; (3) desensitize presynaptic α_2 autoreceptors and downregulate postsynaptic β receptors; (4) antagonize peripheral α_1 and α_2 adrenergic receptors. The net effect of TCAs is to enhance serotonin and norepinephrine neurotransmission in the central nervous system (Buysse 2011). Sedating TCAs also antagonize H_1 histamine receptors and muscarinic M_1 cholinergic receptors.

Antidepressant drugs, which are often used to treat insomnia, are known to affect neuronal plasticity. Antidepressant drugs reverse the structural and functional consequences of stress in the hippocampus and prefrontal cortex, but do not reverse the changes observed in the amygdala (Pilar-Cuéllar et al. 2013). Also, the antidepressant efficacy has been linked to increased levels of brain-derived neurotrophic factors, which in turn may promote hippocampal neurogenesis (Castren and Hen 2013; Lucassen et al. 2010; Wainwright and Galea 2013). Chronic antidepressant therapy induces increased precursor proliferation in the dentate gyrus and increases survival of newborn neurons that functionally integrate into hippocampal circuitry. Synaptogenesis and synaptic elimination are promoted through arborization and pruning of axonal and dendritic branches. Antidepressants also influence plastic regulation for synaptic strength. Information transfers through the active synapses via LTP, while inactive synapses are suppressed via long-term depression. Environmental activity regulates transcription and translation of effector genes involved in neuronal plasticity (Castren and Hen 2013).

Also, cognitive function can be affected by antidepressant medications. In remitted major depressive disorder subjects, a recent study evaluated memory and executive functions in 4 groups of subjects: 50 medicated (29 treated with tricyclic antidepressants (TCAs), 21 with selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors), 19 medication-free subjects, and 31 controls (Nagane et al. 2014). All 3 depressed groups had significantly lower performance for verbal memory compared with controls. Visual memory was worse in both medicated groups compared to controls, while no significant difference was found between controls and the non-medicated group. Only the group treated with TCAs showed a significantly lower performance in cognition compared with controls.

Trazodone, a tetracyclic antidepressant, weakly inhibits serotonin reuptake transporters, but has no effect on dopamine or NE reuptake. Trazodone inhibits serotonin receptors (5-$HT_{1A,}$ 5-$HT_{2A,}$ and 5-HT_{2C}), adrenergic receptors (α_1 and α_2), and histamine receptors (H_1). It has sedative properties and improves subjective sleep quality. Effects on sleep latency, TST, and sleep efficiency are inconsistent; slow-wave sleep is increased; REM sleep is not significantly changed (Buysse 2011).

In cats, trazodone significantly impaired sleep-dependent consolidation of ocular dominance plasticity: Deficits occurred in both the normal depression of V1 (medial occipital lobe) neuronal responses to deprived eye stimulation and potentiation of responses to non-deprived eye stimulation (Aton et al. 2009). These results were hypothesized to be due to trazodone blockade of 5-HT_{2C} receptors during sleep, which impairs the normal strengthening and weakening of synapses in V1 (Aton et al. 2009).

Mirtazapine is a presynaptic α_2 adrenergic reuptake inhibitor; it increases noradrenergic tone through blockade of α_2 adrenergic autoreceptors and heteroreceptors. Enhanced serotonergic neurotransmission is mediated via 5-HT_1 receptors. Mirtazapine is a postsynaptic serotonergic 5-HT_2 and 5 HT_3 antagonists. Mirtazapine has weak muscarinic, anticholinergic, and histaminic (H_1) antagonist effects. It decreases sleep latency, increases TST, and reduces WASO, in adults with and without depression. Mirtazapine is associated with sedation, weight gain, and dry mouth. With acute dosing at 30 mg, mirtazapine prolonged next-day motor reaction and impaired driving performance compared to placebo; sub-chronic administration did not affect performance (Wingen et al. 2005). Similar results were observed in another study comparing effects of mirtazapine 15 mg to trazodone 25 mg: Acute treatment with mirtazapine increased sleepiness and impaired road-tracking performance, but not car-following performance, while trazodone did not impair driving or cognitive performance (Sasada et al. 2013). Mirtazapine enhanced cognitive functions associated with prefrontal cortex in patients with recurrent depression, with 2/3 showing normal values after 6 months of treatment. This improvement did not correlate with the degree of amelioration of depression (Borkowska et al. 2007). Adjunctive mirtazapine added to first generation antipsychotics in a group of schizophrenic subjects improved cognitive function (Stenberg et al. 2010).

Amitriptyline is a potent REM sleep suppressant. Anticholinergic side effects can lead to blurred vision, dryness of the mouth, urinary retention, and orthostatic hypotension. Rapid withdrawal of TCAs can lead to REM rebound and nightmares. Amitriptyline overdose can be fatal within 24 h of ingestion due to cardiovascular toxicity with ECG abnormalities, arrhythmias, and hypotension (Thanacoody and Thomas 2005).

Gabapentin and pregabalin have analgesic and sedative effects; both have been associated with improvement in self-reported sleep measures in patients with painful conditions, such as fibromyalgia, neuropathy, post-surgery, and post-herpetic neuralgia (Buysse 2011). Both drugs do not interact with $GABA_A$ or $GABA_B$ receptors, but may promote GABA production in the CNS. Daily doses of gabapentin range from 300–2,100 mg, while pregabalin doses range from 150–600 mg daily; both are administered in divided doses, with larger doses at night. Side effects include sedation, fatigue, dizziness, ataxia, and less commonly leukopenia.

Tiagabine, an adjuvant anticonvulsant, inhibits GABA transporter GAT_1 and increases the inhibitory actions of GABA (Buysse 2011). Doses of 4–16 mg have been utilized to treat insomnia. Dose-related increase in slow-wave sleep has been reported; effects on TST and WASO are inconsistent. Side effects include dizziness,

nausea, and somnolence. A study comparing the effects of anti-epileptic drugs on associative LTP-like plasticity in the human motor cortex reported that gabapentin administration has no effect on LTP-like motor cortical plasticity, while tiagabine use resulted in non-significant trends toward reduction of long-term potentiation-like motor cortical plasticity (Heidegger et al. 2010).

Gaboxadol is a novel selective extrasynaptic agonist of $GABA_A$ receptors that contain α_4, α_6, and delta subunits. Gaboxadol has peak levels within 30 min of intake and has a half-life of 1.5–2 h. Doses of 5–15 mg reduced LPS and WASO, increased TST, and increased slow-wave sleep duration without significant effects on duration of Stage 1, Stage 2, or REM sleep (Deacon et al. 2007). Cognitive testing the next day after gaboxadol administration did not show any significant impairment in the cognitive drug research test battery results (Deacon et al. 2007). Gaboxadol did not alter information processing, psychomotor performance, and memory measured 12–24 h after treatment (Boyle et al. 2009; Deacon et al. 2007). On the other hand, animal studies suggest that Gaboxadol may have cognitive effects that depend on the duration of the treatment. While acutely increasing $\delta GABA_A$ activity in mice may result in memory impairment, long-term treatment may improve memory (Whissell et al. 2013). Particularly, pre-treatment with gaboxadol for 7 days improved discrimination memory (Whissell et al. 2013). Such memory enhancing effects are associated with an increase in the generation of new neurons in the hippocampus, which are thought to contribute to spatial memory, recognition memory, and fear memory (Marín-Burgin and Schinder 2012).

Clonidine, a central α_2 agonist, decreases adrenergic tone. It is commonly prescribed for sleep-onset delay in children and for ADHD symptoms. Peak effects occur at 2–4 h and interrupted sleep may occur as levels drop (Owens and Mindell 2011). If tolerance develops, dosage may be increased. Clonidine decreases REM and slow-wave sleep; discontinuation can precipitate REM rebound or slow-wave sleep rebound. Side effects include hypotension, bradycardia, anticholinergic effects, and dysphoria. This medication should be avoided in diabetic patients and patients with Raynaud's syndrome.

Positron emission tomography measurements of brain activity in healthy subjects following clonidine infusion showed reduced functional strength of fronto-thalamic connections and pathways to and from the visual cortex at rest (Coull et al. 1999). While performing attentional tasks, clonidine increased the modulatory effects of frontal cortex on projections from locus coeruleus to parietal cortex (Coull et al. 1999). Clonidine improved memory and task performance in Korsakoff's amnesia patients and schizophrenic patients (Mair and McEntee 1986; Fields et al. 1988). In schizophrenic patients, reduced pre-pulse inhibition of the startle reflex may be a manifestation of reduced filtering of sensory information, which can lead to cognitive fragmentation, hallucinations, and delusions. Clonidine improved and normalized these pre-pulse deficits (Oranje and Glenthoj 2013). Clonidine also facilitated mnemonic functions and spatial working memory in parkinsonian patients, although planning, single spatial span memory, or spatial recognition memory did not improve (Riekkinen and Riekkinen 1999).

Quetiapine is an atypical anti-psychotic that is commonly used to treat insomnia in patients with psychiatric illness and dementia and for insomnia in prisoners and military personnel (Anderson and Vande Griend 2014). It is an antagonist with strong affinity for H_1 receptors, moderate affinity for 5-HT_{2A} receptors and 5-HT_{1A} receptors, weak affinity for adrenergic α_1 and α_2 receptors, dopamine receptors D_1 and D_2, and has no appreciable affinity for muscarinic, cholinergic, or benzodiazepine receptors. Its half-life is 2–3 h. Although antipsychotic dosages range from 150–800 mg daily, off-label use for insomnia ranges from 25–200 mg. Twenty-five mg of quetiapine reduced mean sleep latency and increased mean TST in 13 healthy men compared to placebo group; although a trend for improvement was demonstrated, statistical improvement was not demonstrated (Tassniyom et al. 2010). Quetiapine (25, 100 mg) improved subjective measures of sleep quality, sleep latency, and sleep continuity in 14 healthy men. Polysomnography showed increased TST, increased sleep efficiency, and increased percentage for Stage 2 sleep; periodic leg movements of sleep were significantly increased with the 100 mg dose (Cohrs et al. 2004). Side effects include dry mouth, weight gain, and increased blood sugar.

Neuronal and synaptic plasticity may be altered with quetiapine. Hippocampal neuronal cultures in rats showed that atypical antipsychotics (including quetiapine) up-regulated synaptic proteins and dendritic outgrowth (Park et al. 2013). fMRI studies in schizophrenics before and after 12 weeks of quetiapine monotherapy showed that treated patients had a significant increase of activation in the ventrolateral prefrontal cortex, lingual gyrus, and right precuneus. Behavioral measurement of responses including reaction time and performance demonstrated slight improvements, but these did not reach statistical significance (Meisenzahl et al. 2006).

3.2.5 Unregulated Agents for Insomnia

Alcohol is used as a sleep-aid by 6–13 % of the US population. Unregulated health supplements used to improve sleep include valerian root (Valeriana officinalis), kava-kava (Piper methysticum, lavender, hops (Humulus lupulus), passionflower (genus Passiflora), lemon balm (Melissa officinalis), and skullcap (genus Scutellaria) (Weeks 2009). Extracts of magnolia and phellodendron bark have mild sedative effect. Supplements, such as GABA, theanine, tryptophan, and 5 hydroxytryptophan are purported to promote relaxation (Weeks 2009). As these supplements are unregulated, purity and concentration may vary across formulations. A 4-way crossover study in 9 healthy subjects compared valerian (500, 1,000 mg) to triazolam 0.25 mg and placebo. Interestingly, valerian did not affect either cognitive or psychomotor performance at the doses used, while triazolam had detrimental effects on cognitive processes (Hallam et al. 2003). A review of neurocognitive effects of kava evaluated 10 studies (7 acute, 3 chronic use) and concluded that majority of the studies did not demonstrate replicable significant negative effects on cognition (LaPorte et al. 2011). One acute study found that kava

improved visual attention and working memory processes, while another showed that body sway was increased. One chronic study found that kava significantly impaired visual attention during high cognitive demand (LaPorte et al. 2011).

3.2.6 Hypocretin (Orexin) Antagonists

In recent years, the hypocretin/orexin system has received a great deal of attention as a target for insomnia treatment. Hypocretin-1 and hypocretin-2 (also known as orexin-A andorexin-B) are neuropeptides produced in the lateral hypothalamus. Hypocretin neurons receive input from nuclei mediating stress, autonomic tone, reward and motivation, as well as the circadian clock responsible for the timing of sleep and wakefulness. The hypocretin cells integrate these various inputs to promote many aspects of arousal via two different receptors (HcrtR1 and HcrtR2) (Scammell and Winrow 2011). Hypocretin neuronal activity oscillates during the active phase but is low during the normal sleep period. Hypocretin antagonists promote the transition between arousal and sleep by inhibiting the orexin-mediated wakefulness system that is responsible for the transition between arousal and sleep. Single hypocretin receptor antagonists have been studied (SB-334867 binds to HcrtR1 and JNJ-10397409 binds to HcrtR2), but only the dual hypocretin receptor antagonists (DORA) are undergoing FDA phase trials (Winrow and Renger 2014).

On August 13, 2014, the US Food and Drug Administration approved suvorexant as the first drug in its class to treat insomnia. Suvorexant, a potent HcrtR1-HcrtR2 antagonist, was approved at 4 different strengths (5, 10, 15, 20 mg) to treat sleep-onset and sleep-maintenance insomnia. Median peak plasma levels occur 2 h after ingestion; it is extensively metabolized primarily by CYP3A4 with some contribution from CYP2C19. The mean terminal half-life is about 12 h, while the drug's accumulation under the curve (AUC) and maximum concentration (Cmax) is about 1.2–1.6 h at steady state. Oral clearance is about 20 % lower in women than in men. The concentration of suvorexant 9 h after dosing is 15 % higher in the elderly compared to the non-elderly and is 20 % higher in obese patients than in those with normal BMI (FDA 2013).

Three randomized, double-blind, placebo-controlled studies evaluated suvorexant at varying doses and with different study designs as a treatment for insomnia (Sun et al. 2013; Herring et al. 2012; Michelson et al. 2014). Suvorexant improved sleep maintenance with reduced WASO, increased sleep efficiency and TST, and improved sleep latency (Sun et al. 2013; Herring et al. 2012; Michelson et al. 2014). No statistically significant difference was found on EEG frequency bands, including delta activity based on power spectral analysis (Sun et al. 2013). All doses were superior to placebo, based on TST. All doses (10–80 mg) were superior to placebo in reducing WASO, but there was a dose response related to reducing sleep latency. Higher doses (40, 80 mg) were more consistently effective, while the 10 mg dose was the least effective across measures (Herring et al. 2012). Based on the analysis of combined data from 3 studies submitted including concentration analyses results,

the FDA officials concluded that there was no dose or concentration response based on objective sleep latency values; they opined that there was little evidence to suggest that higher doses were substantially superior to 10–15 mg dose (FDA 2013).

Suvorexant was generally well tolerated, but higher doses (40, 80 mg) showed higher rates of side effects compared to lower doses (10, 20 mg) (Michelson et al. 2014). Side effects reported included somnolence, headache, dizziness, abnormal dreams, upper respiratory or urinary tract infection, and increased alanine aminotransferase. Somnolence was present in 13 % of suvorexant group [Michelson et al. 2014) and was more frequent at higher doses [40, 50, 80, 100] mg (Sun et al. 2013; Michelson et al. 2014)]. Higher doses (40 or 80 mg) were associated with sleep paralysis ($n = 2$) and visual hallucinations ($n = 2$) (Michelson et al. 2014). In the above 3 studies, there were no reports of cataplexy or somnambulism side effects.

The FDA-approved lower doses of suvorexant than were utilized initially in clinical trials due to safety concerns regarding next morning sedation, driving performance, and suicidal ideation (FDA 2013). High-dose suvorexant had an eightfold increase in somnolence compared to low doses; somnolence incidence rose for at least 60 days from start of therapy. A formal driving study showed next-morning impaired performance at doses of 20 and 40 mg with increased standard deviation of lane position (defined as SDLP ≥2.4 cm ∼ the equivalent of a blood alcohol level of 0.05 %) (FDA 2013). Four women discontinued testing due to somnolence at 40 mg. Suicidal ideation/behavior was noted in 8/1,268 patients compared to 0/1,012 placebo subjects. Although an adjudicating committee (Michelson et al. 2014) ruled on 45 reported cases, no cataplexy was identified: The FDA consultant believed there was at least 1 subject who had probable cataplexy (on 40 mg of suvorexant, laughing triggered leg weakness lasting 5–30 s and was associated with somnolence).

Several new hypocretin antagonist drugs are still in development. GSK's HcrtR1-HcrtR2 antagonist SB-649868 has undergone 6 Phase I trials and has completed 1 Phase II trial to treat insomnia (Bettica et al. 2012a, b, c). Two phase I dose escalation trials in 103 men (10–80 mg single dose, 5–30 mg repeat doses) reported an estimated half-life of 3–6 h, dose-dependent CYP34A4 inhibition (mild at 5 mg, strong at 30 mg), and somnolence/fatigue at higher doses (60, 80 mg) (Bettica et al. 2012a, b, c). Next-morning test was negative for residual cognitive effects, but fatigue was observed (60, 80 mg) (Bettica et al. 2012a, b, c). In a Phase II study, when compared to placebo, all doses of SB-649868 (10, 30, 60 mg) administered 90 min before bedtime significantly reduced sleep latency, but only higher doses (30, 60 mg) improved sleep maintenance (WASO). SB-649868 increased TST from 22–70 min, slightly reduced percentage of Stage I and slow-wave sleep, and dose-dependently increased REM sleep percentage (Bettica et al. 2012a, b, c). Most common adverse events included headache, dry mouth (dose-dependent), nasopharyngitis, and dose-dependent fatigue. There were no reported symptoms of hallucinations, sleep paralysis, or cataplexy. Next-day residual effects as assessed by cognitive tests and auditory verbal learning test gave mixed results except for reduction in the number of correct words at the end of the test (Bettica et al. 2012a, b, c).

There is some evidence from controlled studies in animals that hypocretin antagonists may affect neuronal plasticity and cognitive function. Compared to $GABA_A$ receptor agonists zolpidem and eszopiclone, a study in rat and rhesus monkeys concluded there is a wider therapeutic margin for sleep versus cognitive impairment using DORA. A wider therapeutic margin was shown by the expression of hippocampal activity-regulated cytoskeletal-associated protein, an immediate early gene product involved in synaptic plasticity (Uslaner et al. 2013).

Abuse potential is also a consideration in choosing a pharmacologic agent for treating chronic insomnia. Hypocretin signaling is an important element in the response to the reward circuits in the central nervous system that is activated by drugs of abuse. An experiment in rats showed that DORA prevented transcriptional and behavioral plasticity resulting from stimulant (amphetamine) exposure, particularly in the ventral tegmental area (Winrow et al. 2010, 2011) and also attenuated the capacity of nicotine to induce reinstatement of extinguished responding for a reinforce. These findings could be beneficial as it may prevent drug-induced plasticity and drug-relapse in substance abusers.

4 Narcolepsy and Its Pharmacological Therapy

Gelineau in 1880 first coined the term narcolepsy to describe a pathologic condition characterized by irresistible episodes of sleep of short duration recurring at close intervals, at times accompanied by falls triggered by strong emotion (Guilleminault and Abad 2009). Narcolepsy refers to a syndrome characterized by excessive daytime sleepiness, disturbed nocturnal sleep, and pathologic manifestations of REM sleep. These REM sleep abnormalities include sleep-onset REM periods, cataplexy, sleep paralysis, and hypnagogic hallucinations. Narcolepsy is newly categorized into narcolepsy type 1 (previously called narcolepsy with cataplexy) and narcolepsy type 2 (narcolepsy without cataplexy) to highlight the concept that the absence of hypocretin (orexin) is a fundamental marker of the disorder (American Academy of Sleep Medicine 2014).

4.1 Narcolepsy, Brain Plasticity, and Cognitive Function

The hypocretin system is critical in promoting wakefulness: Hypocretin deficiency is present in narcolepsy, and excessive somnolence is one of the hallmarks of this disorder. The neurons synthesizing hypocretin are affected by nutrition and behavioral states, and these factors lead to synaptic plasticity and reorganization of synaptic architecture in hypocretin neurons (Gao and Wang 2010). Results from TMS studies in narcolepsy patients showed a significant increase of relaxed

threshold and active threshold, while central short period and central motor conduction time were unaffected; paired TMS showed a significant increase of short intracortical inhibition, and short intracortical facilitation was unchanged (Civardi et al. 2009). These changes in excitability of intrinsic circuits in motor cortex observed in narcolepsy patients could correlate with the deficit of hypocretin/orexin system, through a reduction of histaminergic hypothalamic inhibitory projections to cortical GABAergic neurons (Civardi et al. 2009).

TMS findings in drug-naive narcolepsy patients with or without cataplexy differ from those in treated patients. Resting motor threshold is a marker of the excitability of a central core of corticospinal motor neurons, excitatory interneurons, and target spinal motor neurons. A TMS study was performed on narcolepsy patients who were on central nervous stimulants (methylphenidate and/or modafinil) for EDS and either typical or atypical TCAs (clomipramine, fluoxetine) (Vijayakumari et al. 2013). Increased resting motor threshold was present in drug-naive narcolepsy patients compared to controls, suggesting lower motor cortex excitability and enhanced excitability of inhibitory circuits (Vijayakumari et al. 2013). With treatment, resting motor threshold became similar to that in controls. The change in resting motor threshold scores was greater in younger narcolepsy patients (Vijayakumari et al. 2013). The cortical silent period pre-treatment of narcolepsy was significantly higher compared to controls, suggesting reduced excitability of cortical networks in human narcolepsy. After treatment, the central silent period is decreased in narcoleptics but still significantly differed from the controls. It is hypothesized that the first part of central silent period may be due to spinal inhibitory mechanisms, while the second part may be of cortical origin (Vijayakumari et al. 2013). Another study using modafinil showed significant shortening of the central silent period with treatment, suggesting increase in motor excitability (Joo et al. 2010). Another parameter tested with TMS is central motor conduction time, which is an indirect measure of maximum conduction velocity of corticospinal axons. Central motor conduction time did not differ before and after treatment, nor was it different from controls (Vijayakumari et al. 2013).

A review of neuroimaging studies in narcolepsy with cataplexy cited the following results: (a) Hypothalamic anatomical and functional abnormalities are consistently found, compatible with loss of hypocretinergic neurons; (b) structural alterations are seen in the hypothalamus and limbic system particularly the amygdala and abnormal neural responses are noted in these areas during disruption of emotional processing associated with cataplexy; (c) involvement of the ventral tegmental area and nucleus accumbens in narcolepsy with cataplexy is demonstrated by both neurostructural changes and altered neural response during reward processing; (d) functional and structural changes in hippocampal and various cortical regions (particularly fronto-temporal) may relate to specific mood/cognitive disturbances seen in narcolepsy/cataplexy; and (e) reduced thalamic volume, perfusion, and glucose metabolism in narcolepsy/cataplexy might relate to diminished alertness and disrupted sleep architecture in these patients (Dang-Vu 2013).

4.2 Narcolepsy Treatment

Current therapy for narcolepsy is symptom-based. Scheduled naps can combat sleepiness, but are seldom sufficient as primary therapy.

4.2.1 Modafinil

Modafinil is standard therapy for hypersomnia with narcolepsy, with doses ranging from 200–600 mg daily. Armodafinil, its R-enantiomer, significantly improved daytime sleepiness in narcolepsy patients, as shown in short-term randomized trials as well as in a multicenter trial lasting >12 months (Black et al. 2010). Starting dose was 100 mg, and dose was titrated to a maximum dose of 250 mg daily.

Modafinil's mechanism of action remains unclear, but is postulated to involve various neurotransmitter systems including dopamine, norepinephrine, histamine, glutamate, GABA, serotonin, and hypocretin/orexin. Modafinil increases sleep latency in the multiple sleep latency tests in narcoleptic patients and shift workers and also prolongs sleep latency in the maintenance of wakefulness test in narcoleptic patients and sleep apnea patients. Side effects include headache, insomnia, nausea, dry mouth, vomiting, tachycardia, palpitations, and rarely Steven–Johnson syndrome. Armodafinil has similar side effects, with headache in 25 %, nasopharyngitis in 17 %, insomnia in 14 %, and upper respiratory tract infection in 10 % of patients with excessive daytime sleepiness due to narcolepsy, sleep apnea, and shift work disorder (Black and Hirshkowitz 2005). Cardiovascular side effects were present in 5–9 % of all patients treated with armodafinil. Hypertension (6 %) and palpitations (3 %) were the most common adverse cardiovascular events reported (Black and Hirshkowitz 2005). Patients using modafinil or armodafinil who are on oral contraceptives are advised to use another form of contraception, while on modafinil and for 1 month after discontinuation, since modafinil can increase metabolism of oral contraceptives by inducing hepatic cytochrome P450 enzymes.

Modafinil improved information processing speed and increased energetic resources in the prefrontal region as demonstrated by low-resolution brain electromagnetic tomography (Saletu et al. 2009).

4.2.2 Amphetamines

Stimulants, such as amphetamine, methamphetamine, dextroamphetamine, and methylphenidate, are highly effective for sleepiness, but they are habit forming and have addictive potential.

At low doses, amphetamines increase catecholamine (dopamine and NE) release and inhibit dopamine and NE reuptake from presynaptic terminals. Presynaptic modulation of the dopaminergic system mediates EEG arousal effects. At higher doses, amphetamine increases release of serotonin and inhibits vesicular

monoamine transporter. Use of these stimulants may result in tolerance and increased potential for addiction. Acute side effects include increase in systolic and diastolic blood pressure, anorexia, dryness of the mouth, palpitations and tachycardia, insomnia and restlessness, headaches, agitation, confusion, and dysphoria. Chronic use can lead to irritability and bad temper, profuse sweating, headaches, orofacial dyskinesia, chorea, and tremor. Methamphetamine can be neurotoxic at high doses.

Methylphenidate, an N-methyl derivative of amphetamine, has a shorter half-life and milder side effects. Side effects include psychosis, seizures, and anorexia; overdose can result in arrhythmias and sudden death.

The effects of prescription drug stimulants on plasticity remain under investigation. Amphetamine has a biphasic effect: Low doses enhance LTP in the prefrontal cortex, while high doses impair it (Xu et al. 2010). This may explain the improved cognition seen with low-dose amphetamine (0.25 mg/kg) administered to healthy subjects before performing a working memory task while undergoing fMRI scanning (Mattay et al. 2000) and improved reaction time on spatial working memory and Stroop tasks in schizophrenics and control subjects (Barch and Carter 2005). In contrast, chronic high-dose stimulant use (amphetamine, methylphenidate) is associated with impaired verbal learning and memory capacities (Reske et al. 2010). Repetitive use of amphetamine suppresses intrinsic neuronal excitability in the ventral subiculum, a part of the hippocampus that activates dopamine transmission; ventral subiculum synaptic output may be diminished, leading to impairment of ventral subiculum-dependent associative learning (Cooper et al. 2003). A review of 40 placebo-controlled studies of methylphenidate use in ADHD concluded that methylphenidate improved performance on planning/cognitive flexibility, attention/vigilance, and inhibitory control tasks in 71.4, 70.6, and 69.7 % of studies, respectively. Also, a total of 58.3 and 50 % of the studies that evaluated the effect of methylphenidate on tasks of memory and working memory/divided attention, respectively, noted improvement (Pietrzak et al. 2006).

4.2.3 Caffeine

Caffeine, an adenosine receptor antagonist, is the most common psychomotor stimulant used by the general population to improve alertness, mood, and cognitive performance. Sixty-three to eighty-two percent of narcolepsy patients use caffeine (Won et al. 2014). Caffeine tablets are available in 50–200 mg doses, and caffeinated beverages vary widely in content from 5–250 mg, with energy drinks containing as much as 505 mg. Peak levels occur within 0.5–1 h, and half-life is from 3–5 h. When taken before sleep, it delays sleep onset, decreases slow-wave sleep, decreases TST, and reduces sleep efficiency (Buysse 2011). High doses can lead to muscle twitches, cramps, and nervousness.

In rats, chronic low-dose caffeine treatment prevented short-term memory impairment and early LTP TP in acutely sleep-deprived rats (Alhaider et al. 2010). Low doses of caffeine (12.5, 50, 100 mg) enhanced task performance tests for

simple reaction time and a rapid visual information processing task; all doses affected cognitive performance with a flat dose response effect for the above doses (Smit and Rogers 2000). In 12 healthy subjects, lower dose caffeine (250 mg) enhanced performance on the digit symbol substitution test and a tapping speed test compared to placebo, while high-dose caffeine (500 mg) produced less performance enhancement than the lower dose (Kaplan et al. 1997). Subjective effects were better (elation, peacefulness, pleasantness) with the 250 mg dose, while unpleasant effects (nervousness, anxiety, excitement, irritability, restlessness, palpitations, nausea) were more frequent in the 500 mg dose (Kaplan et al. 1997).

4.2.4 Histaminergic Drugs

Drugs which block histamine H3 autoreceptors (Pitolisant) increase brain histamine and enhance wakefulness in narcolepsy patients. The H3 receptors autoinhibit histaminergic neurons, thereby modulating the synthesis and release of histamine. As presynaptic heteroreceptors, H_3 receptors also control the release of acetylcholine, glutamate, GABA, and peptides (Lin et al. 2011). Based on studies in KO mice, it is hypothesized that H3 R antagonists disinhibit H3 autoreceptors, thereby enhancing synaptic histamine, with activation of postsynaptic H1 receptors, thereby promoting wakefulness. In humans, administration of H3 receptor inverse agonist/antagonist pitolisant (BF2-649) increases histamine and noradrenaline neuronal activity and promotes wakefulness (Weisler et al. 2012; Schwartz 2011; Lazewska and Kiec-Konowicz 2010; Dauvilliers et al. 2013). Pitolisant (individualized dose 10, 20, 40 mg/day) improved somnolence in 26 adult narcolepsy patients and reduced Epworth sleepiness scale (ESS) scores by $\sim$5 units; cataplexy frequency also decreased in those who continued to take it optionally for 9 months. Pitolisant has also been successfully used to treat refractory hypersomnia in a few cases of narcoleptic teenagers (Inocente et al. 2012).

A randomized study of narcolepsy patients compared ESS scores of 32 patients on pitolisant (10, 20, 40 mg) to 33 patients on modafinil (100, 200 mg) to 30 patients on placebo. Over 8 weeks, ESS scores declined by -3.4 ± 4.2 in placebo versus -5.8 ± 6.2 in pitolisant group, and -6.9 ± 6.2 in the modafinil group (Dauvilliers et al. 2013). Adverse events for pitolisant were headache (35 %), insomnia, abdominal pain, nausea, and diarrhea. For modafinil, adverse effects included abdominal pain, withdrawal such as symptoms, lymphadenopathy, and inner ear dysfunction (Dauvilliers et al. 2013). A Phase III trial NCT01789398 (Harmony IV) of narcolepsy patients with pitolisant added to oxybate is ongoing. Another trial NCT01800045 is recruiting subjects to evaluate frequency of cataplexy attacks with pitolisant use compared to placebo.

Pitolisant also reduced ESS by $\sim$6 units in 12 obstructive sleep apnea (OSA) patients who received 40 mg daily for 3 days (Schwartz 2011). Pitolisant had a favorable risk/benefit ratio in 23–38 % of idiopathic hypersomnia and symptomatic hypersomnia patients who were refractory to the usual stimulants; however, mean

ESS scores only decreased by 1.5 units in idiopathic hypersomnia patients (Leu-Semenescu et al. 2014).

Other H3 antagonists are still in development. APD916's Phase I trial in 24 healthy volunteers was a randomized, double-blind, placebo-controlled study using doses of 1, 3, and 5 mg of APD916. APD916 had a half-life of approximately 50 h. Abnormal dreams, visual, and tactile hallucinations were reported at the 3 and 5 mg doses, and insomnia was common at the 1 mg dose.

GSK 189254, a potent H3 antagonist, increased wake, reduced slow-wave sleep, and decreased paradoxical sleep in rats. A safety and dose escalation multicenter trial NCT 00366080 trial of GSK 189254 was terminated but the reason for termination was not specified.

4.2.5 Antidepressants, Serotonergic Drugs, and Monoamine Oxidase Inhibitors

TCAs such as imipramine and SSRIs such as venlafaxine and reboxetine may be effective treatments for cataplexy, sleep paralysis, and hypnagogic hallucinations.

TCA's inhibit reuptake of catecholamines, suppress REM sleep, and increase muscle tone. Abrupt withdrawal from TCAs can result in rebound, severe cataplexy.

SSRIs inhibit serotonin reuptake in the presynaptic cleft and also inhibit REM sleep. Noradrenergic reuptake inhibitors, such as venlafaxine, reboxetine, and duloxetine, have also been utilized to treat cataplexy, sleep paralysis, and hypnagogic hallucinations.

Ritanserin, a 5-HT_2 receptor blocker, may be effective as an add-on drug at doses of 5–10 mg/day to combat sleepiness in narcolepsy. Ritanserin increases NREM slow-wave sleep. Selegiline, a monoamine oxidase B inhibitor, at doses of 20–40 mg may be effective treatment for cataplexy and daytime sleepiness, but has potential drug and diet interactions (Morgenthaler et al. 2007).

4.2.6 Sodium Oxybate

Sodium oxybate (SXB) is the sodium salt of gamma hydroxybutyrate (GHB) that is effective for the treatment of cataplexy, daytime sleepiness, and sleep disruption (Morgenthaler et al. 2006); it may be effective for the treatment of hypnagogic hallucinations and sleep paralysis.

GHB is a metabolite that is concentrated in the hypothalamus and basal ganglia. GHB is also a precursor of GABA and may act as a neurotransmitter or neuromodulator; it has high-affinity binding with GHB receptors in the hippocampus and cortex (Van Amsterdam et al. 2012). GHB inhibits glutaminergic neurotransmission in neocortical and hippocampal neurons. At low doses, GHB increases glutamate release; however, supraphysiological or pharmacological doses lead to GHB receptor saturation and desensitization with decreased glutamate release

(Van Amsterdam et al. 2012). GHB has 3 types of interactions with the GABAergic system: as a precursor of GABA, as a promoter of GABA release, and as a low-affinity $GABA_B$ receptor agonist (Snead and Gibson 2005). GHB has a biphasic effect in rats: Low doses increase dopaminergic firing, while high doses inhibit dopaminergic cell firing (Diana et al. 1991). GHB is a weak but selective; at pharmacologic doses, GHB may interact with the endogenous opioid system and increase serotonin turnover. It increases slow-wave sleep, reduces arousals, and has a variable effect on REM latency and REM duration. At doses of 6–9 g SXB, cataplectic episodes decrease in frequency and daytime sleepiness improves. SXB requires split dosing at night. Common side effects include dizziness, headache, nausea, somnolence, confusion, and nocturnal enuresis.

In animal studies, GHB impaired learning and performance of memory tasks (Van Amsterdam et al. 2012). In rats, GHB administration had a biphasic effect: Low dose (10 mg/kg × 15 days) produced more neuronal loss in the prefrontal cortex and hippocampal CA1 regions compared to higher dose (100 mg/kg) (Pedraza et al. 2009). It is postulated that low doses of GHB increase release of glutamate with cytotoxicity on neighboring neurons, while higher doses initiate GABA mechanisms that inhibit the increased glutamate release, thereby exerting a protective effect on glutamatergic neurotoxicity (Mamelak 2007). Of concern also, is the age-specific effect of GHB (adolescent rats are more sensitive to GHB-induced cognitive effects), which are due to neuroadaptations in glutamatergic neurotransmission in the frontal cortex (Sircar et al. 2011). Animal studies, including proteomic and genomic studies, suggest that GHB increases oxidative stress, possibly inducing neurodegeneration (Van Amsterdam et al. 2012). Also, up- or downregulation of several proteins and genes may affect cognition, apoptosis, or neuroprotection (Van Amsterdam et al. 2012). A study in mice demonstrated accelerated functional recovery after focal cerebral ischemia by altering expression of several neuroplasticity related genes in the striatum (c-jun and neurocan genes) (Gao et al. 2008).

In humans, acute administration of GHB induced amnesia and impaired working memory and episodic memory in drug abusers and healthy volunteers (Carter et al. 2009). Heavy users of GHB report severe memory problems and case studies have reported short- and long-term memory impairment. However, the long-term effects of GHB on cognition in humans still need systematic investigation.

4.3 Treatment of Narcolepsy in Children

In a retrospective study of 51 children with narcolepsy who had been followed at Stanford Sleep Disorders Clinic from 2001 to 2009 or had participated in research with follow-up over a mean of 4.6 years, different medications including methylphenidate, protriptyline, amitriptyline, imipramine, clomipramine, fluoxetine, paroxetine, escitalopram, sertraline, atomoxetine), bupropion, and duloxetine were

tried, but rarely continued. The most utilized and continued medications were modafinil (84 %), sodium oxybate (79 %), and venlafaxine (68 %) (Aran et al. 2010). In the past 4 years, atomoxetine, a noradrenergic reuptake blocker, has been frequently used in children for its alerting and anti-cataplectic effect. For children weighing less than 70 kg, start at 0.5 mg/kg/day and increase after minimum of 3 days, as needed, to a maximum of 1.2 mg/kg/day given in a single dose. For adolescents, start at 25 mg/day and increase after minimum of 3 days, as needed, to a maximum of the lesser of 1.4 mg/kg/day or 100 mg/day. Modafinil was effective in treating sleepiness but did not affect cataplexy. Sodium oxybate (off-label use) was effective for cataplexy and for sleep consolidation. Starting dose for SXB was 60–90 mg/kg/day, administered at night in split dosing (1/2 at bedtime and 1/2 administered 2.5–4 h later) and titrated every 1–2 weeks to efficacy or development of side effects; maximal dose was 180 mg/kg/day, not to exceed 9 g/day. Urinary incontinence was not uncommon at the start, prompting dose reduction and slower escalation of dosage. Almost 20–25 % of children treated with SXB lost weight, while those on venlafaxine or modafinil did not. Children with narcolepsy and SDB were treated with CPAP therapy, in addition to their narcolepsy treatment regimen.

5 Restless Legs Syndrome and Its Pharmacological Treatments

Restless legs syndrome (RLS) is a neurologic disorder present in 4–7 % of individuals characterized by all of the following: An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable/unpleasant leg sensations; beginning or worsening of urge/sensations during periods of rest or inactivity; partial or total relief of urge/sensations by movement (at least as long as activity continues); occurrence or worsening of urge/sensations during evening or night than during the day; and urge/sensations are not solely accounted for as symptoms of another medical or behavioral condition (Allen et al. 2014). The pathophysiology of RLS remains under investigation but altered dopaminergic function and insufficient brain iron have been implicated. It has been proposed that low cellular iron through direct or indirect mechanisms alters one or more components of the dopaminergic synaptic dynamics (postsynaptic receptors, presynaptic receptors, synthesis, release, or uptake of dopamine) resulting in compensatory changes in the other components (Earley et al. 2014).

About 70–80 % of RLS sufferers have primary RLS; secondary RLS can be associated with iron deficiency, end-stage renal disease, pregnancy, diabetes, peripheral neuropathy, and rheumatoid arthritis (García-Borreguero et al. 2007). Symptom severity can be classified into the following: (1) mild/intermittent, (2) moderate, (3) moderately severe/severe, or (4) refractory/intractable (Hening et al. 2009).

5.1 RLS and Plasticity

TMS studies have explored primary RLS pathophysiology. Single TMS pulse may yield a functional assessment of corticospinal conduction: Central motor conduction time is a measure of the integrity of the corticospinal pathways; resting motor threshold provides information about a central core of neurons in the primary motor cortex; and the amplitude of the motor evoked potential is an aggregate measure of the excitation state of output cells in the motor cortex. Motor threshold is increased if a significant part of the corticospinal tract is damaged and is decreased if the corticospinal tract is hyperexcitable. The cortical silent period is a measure of the suppression of the corticospinal output at a cortical level (Lanza et al. 2014). Meanwhile, paired-stimuli TMS studies investigate the intracortical inhibitory and facilitatory mechanisms within the motor cortex (Lanza et al. 2014). Several studies demonstrated significantly reduced short intracortical inhibition, suggesting impairment of cortical inhibitory circuits (Quatrale et al. 2003; Tergau et al. 1999). Using paired associative stimulation protocol by TMS, idiopathic RLS without treatment showed impaired associative sensorimotor plasticity; testing 4 weeks after dopaminergic therapy showed restoration of PAS plasticity (Rizzo et al. 2009). A review of TMS studies (Stiasny-Kolster et al. 2003; Quatrale et al. 2003; Scalise et al. 2006, 2010; Nardone et al. 2006; Rizzo et al. 2009) concluded that the corticospinal tract in RLS patients is unaffected (Lanza et al. 2014). Most studies (Tergau et al. 1999; Entezari-Taher et al. 1999; Quatrale et al. 2003; Scalise et al. 2006, 2010; Nardone et al. 2006; Kutukcu et al. 2006; Gorsler and Liepert 2007; Rizzo et al. 2009, 2010) demonstrated that resting motor threshold is not impaired in RLS patients, except for a study which reported a trend for increased active motor threshold in the tibialis muscle (Stiasny-Kolster et al. 2003) and a study (Gündüz et al. 2012) where decreased active motor threshold from the 1st dorsal interosseous muscle was noted only at night (Lanza et al. 2014). Many studies in RLS patients reported markedly reduced central silent period (Civardi et al. 2004; Joo et al. 2010; Das et al. 2013) that seems to be stable across the day. Treatment with dopamine agonists (Stiasny-Kolster et al. 2003; Kutukcu et al. 2006; Gorsler and Liepert 2007; Lanza et al. 2014) reversed this shortening. Intracortical facilitation is markedly reduced in RLS patients (Tergau et al. 1999; Quatrale et al. 2003; Scalise et al. 2004, 2006, 2010; Nardone et al. 2006; Rizzo et al. 2010).

5.2 RLS Treatment

Symptomatic patients with primary RLS will likely require lifelong treatment, while patients with secondary RLS may have symptoms remit when the underlying condition is resolved.

Non-pharmacologic treatment, particularly good sleep hygiene, applies to all categories of RLS (Hening et al. 2009). Alcohol at bedtime and medications that

can exacerbate RLS should be avoided. The latter includes antihistamines, dopamine antagonists, antidepressants (particularly norepinephrine or SSRIs), antinausea medications (metoclopramide, prochlorperazine), SSRI and SNRI agents, neuroleptics (phenothiazines, olanzapine, risperidone), beta-blockers, lithium, and some anticonvulsants (phenytoin, methsuximide, zonisamide).

The current treatment of choice for RLS consists of dopamine agonists, preferably the non-ergoline derivatives–ropinirole, pramipexole, and rotigotine. Dopamine precursors (levodopa/carbidopa, levodopa/benserazide (not available in the USA), or slow-release formulations are efficacious, have higher chance of augmentation, and are not FDA-approved for RLS. Other categories of medications are less efficacious: opioids, anticonvulsants (gabapentin, pregabalin, valproic acid, carbamazepine, oxycarbazepine, lamotrigine, levatirecetam, topiramate), benzodiazepines (particularly clonazepam), and iron supplements (for patients with low serum iron or if ferritin levels are less than 50 ng/ml) (Hening et al. 2009; Trenkwalder et al. 2008). IV iron dextran is likely efficacious for RLS secondary to end-stage renal disease. Opioid agonists including methadone have been used in severe cases.

Daily medications should be considered for patients with RLS symptoms occurring at least 3 times a week that negatively impact the patients' lives. For moderate to moderately severe RLS, the first-line medications of choice are pramipexole, ropinirole, or rotigotine for nighttime symptoms. If daytime symptoms exacerbate, transdermal rotigotine may be preferred due to longer duration of action. For partial responders, the addition of gabapentin enacarbil or the off-label use of moderate potency opioids, pregabalin, or clonazepam may be considered (Lee et al. 2011). For severe RLS, initial therapy may include non-pharmacologic measures with use of rotigotine during the day; at night, increasing doses of pramipexole, ropinirole, or rotigotine are utilized (Högl et al. 2010; Serafini et al. 2010). Rotigotine (1–3 mg/24 h) transdermal delivery maintains stable plasma levels over 24 h and may be useful in moderate to severe RLS patients who are symptomatic not only at night but also during the day (Bogan 2014).

If needed, gabapentin enacarbil or pregabalin or medium to high-potency opioids or clonazepam may be added (Silver et al. 2011). Post hoc meta-analysis of gabapentin trials suggest that while 600 mg controls subjective RLS symptoms, 1,200 mg once daily dose is recommended to improve the sleep disturbance associated with RLS (Kume 2014). For refractory or intractable RLS symptoms, multiple doses may be needed (evening, bedtime, middle of the night, and if needed daytime dosing). Polytherapy is commonly utilized with a combination of 2–4 drugs from different classes and the use of high-potency opioids. If augmentation occurs, a different medication may be used; if augmentation occurs with levodopa, a dopamine agonist should be substituted. If needed, rotation among 2–3 drugs or drug holidays may be implemented (Hening et al. 2009). Comorbid conditions, such as iron deficiency (history of blood donations, recent surgery) or a review of the patient's medication list (for drugs that exacerbate RLS), have to be pursued in the history, particularly in patients who stop responding to their regimen.

The major complication of long-term dopaminergic therapy is augmentation: Symptoms appear earlier in the day, occur more quickly while the patient is at rest, and may spread to other body parts, including the arms and trunk. Prevention of augmentation is sought by using the lowest dose of the dopaminergic medication that controls symptoms, taking care not to exceed usual recommended dose maximums, and preferring a drug with a longer half-life. If augmentation occurs, then treatment should be switched to a non-dopamine agent or to a dopamine agonist with a longer half-life.

In secondary RLS, iron replenishment should be undertaken in tandem with standard medications, when serum ferritin levels are <50 μg/L. RLS associated with moderate pain (neuropathy) may respond to alpha 2 delta agonists such as pregabalin or gabapentin.

5.3 RLS and Pregnancy

RLS has a severe impact on sleep quality of pregnant women (Hübner et al. 2013). In a prospective study of 541 women, 58 (12 %) had RLS symptoms: 59 % of these women developed symptoms before the 20th week and 45 % had International RLS Scale >20. In this study, women with and without RLS had similar hemoglobin, ferritin, and estrogen levels. Post-delivery and RLS symptoms were still present in 12 (30 %), but symptom severity and periodic leg movements of sleep (documented by Actigraphy) dropped by more than 50 % (Hübner et al. 2013). Reported predictors for RLS during pregnancy include the following: family history of RLS, multiparity, history of RLS during previous pregnancy, anemia, low iron levels, low folate levels, and high estrogen levels (Srivanitchapoom et al. 2014). Non-pharmacological approaches for RLS treatment should be initiated first, including abstinence from caffeine, discontinuation (if possible) of drugs that exacerbate RLS symptoms (anti-emetics, sedating anti-histamines, anti-depressants, neuroleptics). Iron supplements (if iron levels are low) or folic acid supplements may be used. However, if symptoms are severe, a pharmacological approach may be considered after extensive and documented discussion of efficacy/safety issues with the patient. It should be discussed with both parents that the efficacy and safety of various drugs used to treat RLS have not been clearly established and available information is from case studies. Increased risk of pregnancy loss and preterm births has been associated with dopamine agonist use during pregnancy (n = 181), but most of the women studied were treated for hyperprolactinemia (bromocriptine n = 118, cabergoline n = 37, quinagolide n = 18, lisuride n = 7) or Parkinson's disease (pirebedil n = 4, ropinirole n = 1). Prevalence of birth defects and preterm birth was not different when compared to the matched non-exposed group (Hurault-Delarue et al. 2014). In a study of births from 1998 to 2011, the outcome (teratogenicity or fetotoxicity) of 67 exposed pregnancies to levodopa/dopamine agonists was evaluated and 59 of these women completed follow-up (Dostal et al. 2012). Of these

pregnancies, 59 women completed follow-up and reported taking these medications [levodopa (38), pramipexole only (12), levodopa and pramipexole (3), levodopa and ropinirole (1), ropinirole (3), and rotigotine (2)] (Dostal et al. 2012). The study reported results in terms of "numbers of exposed pregnancies/live born children/spontaneous abortions/induced abortions/malformations: levodopa only, 38/29 (one pair of twins)/3/7/3; pramipexole only, 12/9/3/0/0; rotigotine only, 2/2/0/0/0; ropinirole only, 3/2/0/1/0; levodopa combined with pramipexole, 3/3/0/0/0; levodopa combined with ropinirole, 1/1/0/0/0" (Dostal et al. 2012). The anomalies in 3 infants of levodopa-treated mothers included nose deformity, talipes varus, and persistent foramen ovale with a patent ductus arteriosus; outcome in 2 of these infants was influenced by intrauterine malposition (Dostal et al. 2012). Cabergoline, a dopamine receptor agonist, is considered first-line therapy in Europe for RLS, but is not FDA-approved, except as treatment for hyper-prolactinemia. Valve fibrosis had been reported with the high doses used in Parkinson's disease, but not with the lower doses used off-label to treat RLS. With its general safety data and lack of indication for prenatal toxicity from 650 exposed pregnancies, cabergoline has been proposed as another possible treatment for RLS with pregnancy (Dostal et al. 2012). Second-line therapy for RLS, such as valproate, carbamazepine, clonazepam, oxycodone are teratogenic or fetotoxicants (Dostal et al. 2012).

6 Sleep-Disordered Breathing and Its Pharmacological Treatments

OSA is a growing major health hazard that is fueled by the obesity epidemic and an aging population. The prevalence of OSA based on apnea hypopnea index (AHI) ≥5 is 9 % for women and 24 % for men (Young et al. 1993). Sleep-disordered breathing (SDB) is exacerbated during REM sleep. REM-SDB (defined as REM AHI/NREM AHI ≥2) is present in 41 % of women and 21 % of men, with prevalence decreasing with age in women (Koo et al. 2008). The prevalence of REM-SDB increases with severity of OSA: REM-predominant OSA was 43 % if AHI ≥15 versus 14 % if AHI ≥5 (Khan et al. 2013). Inhibition of pharyngeal motor neurons occurs during REM sleep and is a cause of hypoventilation and OSA. Muscarinic receptor-mediated inhibition of the hypoglossal motor pool is an important mechanism for suppression of genioglossus muscle activity during REM sleep. Genioglossus and diaphragm activities were monitored in 34 rats and muscarinic receptor antagonism at the hypoglossal motor pool prevented the inhibition of genioglossus activity throughout REM sleep. This study also demonstrated that muscarinic inhibition of the hypoglossal motor pool is GIRK channel dependent (Grace et al. 2013). Findings from this study may be of significance in the advancement of pharmacologic treatment for OSA, provided side effects of these muscarinic antagonists are tolerable.

6.1 OSA and Plasticity

OSA can result in sleep fragmentation and impaired sleep architecture, as well as in hypoxia and hypercapnia. Altered brain structure and function with OSA can result in cognitive difficulties, including memory impairment, reduction in attention, and abnormalities in executive function (Campana et al. 2010). The neurophysiology of OSA is complex and is investigated through TMS studies and fMRI. However, TMS studies are limited by small sample sizes, with at times, varying results. Also, many of TMS studies are performed in the wake state rather than during sleep, because the loud sound produced by the discharge of the capacitors may rouse the subject from sleep or disturb their sleep. MEP latency in OSA patients did not vary from controls during wake (Civardi et al. 2004; Das et al. 2013), but MEP latency decreased in the dorsal interosseous and genioglossus muscles during tongue protrusion in OSA patients (Sériès et al. 2009). Compared to wake, MEP latency did not change during sleep in 2 studies by the same group, (Melo-Silva et al. 2013) while MEP latency increased in hand muscles only during sleep in another study (Civardi et al. 2004). Resting motor threshold during wake did not significantly vary from controls in 2 studies (Civardi et al. 2004, but was increased in 2 studies (Das et al. 2013; Opie et al. 2013); there was an increased difference between genioglossus and dorsal interosseous during respiration. Motor evoked potentials from diaphragmatic muscles were either absent or reduced in amplitude (only 3/7 MEPs were reported) in 7 OSA patients, and phrenic nerve conduction was abnormal in 4/7 patients (Lu et al. 1998). Central silent period was increased (Civardi et al. 2004; Joo et al. 2010; Das et al. 2013). CMCT was reduced in OSA patients in 1 study (Gao and Wang 2010), but was not significantly different in another study (Das et al. 2013). Neither intracortical facilitation nor intracortical inhibition was significantly different from controls at inter-stimulation intervals of 10–15–20 for the former and 2–3–5 for the latter in 1 study (Joo et al. 2010). Overall, TMS studies in OSA tend to exhibit an increased motor cortex inhibition (Lanza et al. 2014). However, there is a lack of correlation between TMS findings, sleepiness, and cognitive dysfunction in OSA (Nardone et al. 2013a, b).

A combined neuropsychological and brain imaging study (Fluoro-2-deoxy-D-glucose positron emission tomography) with correction for partial volume effects and voxel-based analyses in 16 newly diagnosed sleep apnea patients revealed gray matter loss in the frontal, temporo-parietal cortices, thalamus, hippocampal region, some basal ganglia and cerebellar regions, and mainly in the right hemisphere. Decrease in brain metabolism was noted in the precuneus, middle and posterior cingulate gyrus, parieto-occipital cortex, and prefrontal cortex. Despite these abnormalities, neuropsychological tests only showed minor memory and motor impairments, suggesting that cerebral changes may precede onset of notable neuropsychological impairment (Yaouhi et al. 2009). Functional MRI (fMRI) studies in OSA patients have shown decreased activation in the left postcentral gyrus, cingulate gyrus, inferior parietal lobe, and in the right insula and putamen

(Ayalon et al. 2009). Other fMRI studies in OSA revealed an abnormal pattern of cortical and subcortical local connectivity and an abnormal pattern of brain activity during reward processing (Santarnecchi et al. 2013).

Does OSA lead to structural brain alterations? Voxel-based morphometry in 27 treatment-naïve moderate to severe OSA subjects did not show any significant differences in either gray matter volume or white matter volume compared to controls, although significant negative correlations were observed between nocturnal hypoxemia duration and gray matter volume in bilateral lateral temporal regions. There were no differences between CPAP and sham CPAP treatment effects in these patients (Huynh et al. 2014). However, an (activation likelihood estimation) meta-analysis of neuroimaging in sleep apnea subjects (n = 213) compared to healthy controls (n = 95) concluded that there are significant gray matter reductions in bilateral parahippocampal regions, left temporal lobe (Brodman Area 21), and right frontal lobe (Brodman area 10), which may be related to the neurocognitive processing abnormalities seen in OSA patients (Weng et al. 2014). In another study, fMRI showed significantly reduced cerebrovascular reactivity in patients with moderate to severe OSA compared to healthy control subjects. The abnormal cerebrovascular reactivity did not follow any vascular pattern. In OSA patients, the duration of nocturnal hypoxemia negatively correlated with cerebrovascular reactivity, particularly in medial temporal lobe structures, suggesting a mechanism for hippocampal injury. Perfusion in OSA patients and controls did not differ, and there was no effect of CPAP or sham CPAP on perfusion. Findings from this study suggest a relationship between cerebrovascular reactivity and surrounding neuronal activity. The parahippocampus is significantly involved in memory and learning, while the frontosubcortical systems are responsible for attention and executive functions that involve the prefrontal cortex. The involvement of the hippocampus, prefrontal cortex, and inferior temporal cortex in OSA patients are consistent with working memory impairment that occurs in OSA patients (Prilipko et al. 2014).

Cognitive dysfunction is also an important issue in pediatric OSA patients. A study of 50 OSA children compared to 27 normal controls showed significantly reduced attention and visual fine motor coordination in a battery of neurocognitive tests. Twenty-three of these OSA children underwent voxel morphometry imaging compared to 15 matched controls. Gray matter volume deficit occurred in prefrontal and temporal regions in children with moderate to severe OSA only. Visual fine motor coordination scores had significantly negative correlations with the ratio of gray matter volume over total brain volume (Chan et al. 2014). An fMRI study in 10 children with OSA and 7 matched controls demonstrated that OSA children had greater neural recruitment of brain regions implicated in cognitive control, conflict monitoring, and attention allocation in order to perform at the same level as children without OSA. The severity OSA predicted less sensitivity to harm in the left amygdala, when viewing empathy-eliciting scenarios. This study demonstrated that OSA influences cognitive and empathic processing even when executive functioning is preserved (Kheirandish-Gozal et al. 2014).

6.2 OSA Therapy

Positive airway pressure therapy remains the gold standard of therapy, with alternatives of surgery, or an oral appliance. Medical therapy for OSA includes continuous or bi-level positive airway pressure therapy, weight reduction in overweight/obese patients, positional therapy, supplemental oxygen, and pharmacotherapy. It is important to realize that current pharmacotherapy represents only adjuvant therapy for OSA. The goals of pharmacotherapy in OSA are as follows: (1) to reduce or modify risk factors for OSA (nasal congestion, reduced estrogen, high testosterone levels), (2) treat any underlying predisposing metabolic diseases (acromegaly, hypothyroidism, obesity), (3) treat residual daytime sleepiness, and (4) treat associated hypertension and lipid disorders.

Ventilatory stimulants are not advised for use in OSA. Methylxanthine derivatives (theophylline, aminophylline, and caffeine) reduce TST and sleep efficiency and do not significantly change the frequency or duration of obstructive apneas (Veasey et al. 2006). Naloxone, an opiate antagonist, does not improve AHI nor does it improve associated oxygen desaturation seen in obese sleep apnea patients (Guilleminault and Hayes 1983). Doxapram, a respiratory stimulant that affects peripheral chemoreceptors, slightly improves average oxyhemoglobin desaturation and reduces apnea length, but does not affect the frequency of apnea (Suratt et al. 1986). Baclofen, a GABA β agonist and glutamine antagonist, depresses central respiratory drive, increases upper airway obstruction, and increases arousal threshold to apneas (Finnimore et al. 1995). Acetazolamide, a carbonic anhydrase inhibitor, stimulates ventilation by inducing metabolic acidosis. Administration of acetazolamide has variable effects on AHI. Side effects include paresthesias, tinnitus, dysgeusia, and polyuria (Inoue et al. 1999).

6.2.1 Acetylcholineterase Inhibitors

The prevalence of REM-related SDB varies with age and gender. Inhibition of pharyngeal motor neurons occurs during REM sleep and is a cause of hypoventilation and OSA. Muscarinic receptor-mediated inhibition of the hypoglossal motor pool is an important mechanism for suppression of genioglossus muscle activity during REM sleep. Genioglossus and diaphragm activities were monitored in 34 rats, and muscarinic receptor antagonism at the hypoglossal motor pool prevented the inhibition of genioglossus activity throughout REM sleep. This study also demonstrated that muscarinic inhibition of the hypoglossal motor pool is GIRK channel dependent (Grace et al. 2013, 2014).

Donezepil, a cholinesterase inhibitor, promotes cholinergic transmission (nicotinic and muscarinic). A randomized, double-blind, placebo-controlled trial of donezepil (5 mg daily × 2 weeks, then 10 mg daily for 2 weeks) in 21 male patients with mild to severe OSA reduced mean AHI by ∼9 events/h, REM AHI by ∼8 events/h and improved % time O_2 ≤3 % baseline, lowest oxygen saturation,

desaturation index, and ESS scores in parallel with a reduction in sleep efficiency (Sukys-Claudino et al. 2012).

Physostigmine, an acetylcholinesterase inhibitor, reduced mean AHI from 54 to 41/h, with most of the reduction occurring during REM sleep (mean AHI decreased from 54 to 30/h) in 10 male OSA patients. Sample size was small and results do not warrant use of this agent (Hedner et al. 2003).

6.2.2 REM Sleep Suppressing Agents and Serotonergic Agents

The American Academy of Sleep Medicine (AASM) practice parameters do not recommend the use of TCAs or SSRIs in the treatment of sleep apnea. Paroxetine did not improve hypopnea indices during sleep and only slightly reduced mean apnea index during NREM but not during REM sleep (Kraiczi et al. 1999). During a crossover unblinded trial of fluoxetine and protriptyline in 12 OSA subjects, severe OSA persisted, although mean NREM AHI decreased from 57 ± 9 to 34 ± 6/h for both drugs (Hanzel et al. 1991). Protriptyline did not improve REM-related breathing abnormalities (Smith et al. 1983) although O_2 desaturation events improved from 17 to 9 %.

Clonidine may be helpful in the perioperative management of OSA patients as one study showed significant reduction in propofol dosage required for anesthesia in these patients in addition to an opioid sparing effect (Pawlik et al. 2005).

Mirtazapine had a dose-dependent effect in a study of 12 OSA subjects: At 4.5 mg, there was a 52 % reduction in AHI in all stages of sleep compared to 46 % reduction in AHI on 15 mg. At 30 mg, there was significant increase in AHI. Patients at all doses had significant sedation and weight gain. Mirtazapine is not recommended in the treatment of OHA (Marshall et al. 2008).

6.2.3 Medications for Associated Conditions Predisposing to OSA

Acromegaly: Prevalence of sleep apnea associated with acromegaly varies from 13 to 75 %; sleep apnea severity does not parallel acromegaly disease activity. The effects of growth hormone therapy on sleep-disordered breathing are inconclusive. In 28 acromegalic sleep apnea patients, bromocriptine therapy did not reduce the duration of apneas, nor did it improve AHI (Guilleminault and Hayes 1983). Although RDI was reduced by 28 % in 9 out of 14 patients treated with octeotride, minimum SaO_2 did not significantly improve (Herrmann et al. 2004). Sandostatin LAR, a somastatin analog, improved both acromegaly (improved GH levels) and sleep apnea by reducing mean AHI.

Hypothyroidism: Eleven percent of children with sleep apnea are hypothyroid (Sakellaropoulou et al. 2011), while in adults, the prevalence of associated hypothyroidism varies from 3 to 12 %, and with about 11 % having a subclinical presentation (Lin et al. 1992; Bahammam et al. 2011). Treatment of hypothyroidism resulted in resolution of sleep apnea in 10/12 clinically symptomatic

hypothyroid patients (Jha et al. 2006) and in 2/5 patients who had severe sleep apnea and hypothyroidism (Lin et al. 1992). In subjects with subclinical hypothyroidism, treatment with levothyroxine did not reduce sleep apnea prevalence when compared to the non-treated group, although the latter were sleepier (Resta et al. 2005).

Hormonal therapy: estrogen, progestational agents, androgens, and androgen blockade. Menopause is an independent risk factor for sleep apnea (Bixler et al. 2001). The beneficial effect(s) of hormonal therapy (estrogen alone or estrogen plus progesterone) in treating sleep apnea in postmenopausal women are equivocal, and the sample sizes used in most of the studies are small (Pickett et al. 1989; Keefe et al. 1999; Manber et al. 2003; Saletu-Zvhlarz et al. 2003). Hormonal therapy is not innocuous and carries risks of ischemic strokes, venous thromboembolism, and breast cancer. Given the equivocal benefit and significant risks entailed, the use of HRT in postmenopausal women to treat OSA is not recommended.

Flutamide, an androgen-blocking agent, does not worsen AHI nor does it alter chemoresponsiveness to hypoxia and hypercapnia in patients with moderate to severe OSA (Stewart et al. 1992). High-dose testosterone administered to men with no previous history of sleep apnea increased AHI by >50 % and prolonged hypoxemic episodes (Liu et al. 2003). Patients who receive testosterone should be monitored for symptoms of sleep-disordered breathing.

6.2.4 Medications to Improve Nasal Patency

Eleven percent of sleep apnea patients have associated allergic rhinitis (Canova et al. 2004). Underlying nasal obstruction may contribute to sleep apnea by increasing nasal airway resistance and promoting airway collapse. Both adults and children with OSA benefited from using fluticasone, a nasal steroid spray, with reduction in nasal congestion, and improved AHI (Kiely et al. 2004; Brouillette et al. 2001). Intranasal budesonide administration in combination with a leukotriene (LT) receptor antagonist improved AHI and SaO_2 nadir in children with residual sleep apnea after tonsillectomy and adenoidectomy (Kheirandish et al. 2006). LTD4 and LT receptor antagonists monteleukast, zileuton, and BAY u9733 reduced adenotonsillar proliferation and reduced inflammatory cytokine production (Dayat et al. 2009). These studies demonstrate that some adult and pediatric patients may benefit from treatment of nasal congestion with nasal corticosteroids. Leukotriene receptor antagonist therapy has benefited some children with mild OSA, who are not surgical candidates in addition to children with residual sleep-disordered breathing following T & A. In contrast, nasal decongestant sprays do not improve sleep apnea in adult patients (Braver and Block 1994). There is also the added concern of rebound vasodilation impairing nasal patency with chronic use of short-acting nasal decongestant sprays.

6.2.5 Stimulants

Persistent daytime sleepiness and fatigue can impair daytime function in 5–22 % of sleep apnea patients treated with CPAP (Guilleminault and Philip 1996; Weaver et al. 2007). Stimulants, such as modafinil or armodafinil, are adjunctive treatments to improve sleepiness, vigilance, and quality of life in OSA patients in conjunction with optimized primary therapy for sleep apnea (Black and Hirshkowitz 2005; Roth et al. 2006). Improvements in performance (decreased sleepiness, reduced fatigue, improved episodic secondary memory) have to be balanced against common side effects such as headaches, nervousness and anxiety, insomnia, nausea, and rhinitis.

7 Parasomnias and their Pharmacological Treatments

Parasomnias are disorders of arousal, partial arousal, or sleep-stage transition that manifest as undesirable experiential phenomena or abnormal behaviors during either NREM or REM sleep.

NREM sleep parasomnias are more frequent during childhood but can occur during adult life as well and manifest as confusional arousals, sleep terrors, or sleep walking (somnambulism). The lifetime prevalence for confusional arousals, sleepwalking, and sleep terrors is 18.5, 18.3, and 1–6.5 %, respectively (AASM ICSD III; Ohayon et al. 1999). NREM sleep parasomnia is commonly associated with sleep-disordered breathing, more frequently flow limitation than frank obstructive hypopnea and apneas. In general, the prevalence of parasomnias is higher in depressed individuals and specific combinations of psychotropics pose a higher risk for particular parasomnias: sedative antidepressants and nonbenzodiazepine hypnotics in sleepwalking, and regular zolpidem and antidepressants in sleep-related eating disorders (Lam et al. 2008). Parasomnias have been associated with use of various medications, particularly SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), TCAs, and bupropion.

REM sleep behavior disorder (RBD) is a parasomnia that occurs frequently after age 50 years with a prevalence of 0.38–0.5 % and is associated with sleep-related violence in 2.1 % of affected individuals (AASM ICSD 2014). Neurologic diseases such as Parkinson's disease, multi-system atrophy, dementia with Lewy bodies, and narcolepsy predispose to development of RBD. Various SSRIs/SNRIs, TCAs, MAO inhibitors, and bupropion are also associated with RBD: Specific drugs that have been implicated include paroxetine, fluoxetine, citalopram, sertraline, and venlafaxine. Most cases of acute RBD respond to withdrawal of the offending drug. For chronic RBD, clonazepam at doses ranging from 0.5 to 2 mg is efficacious. Melatonin at doses up to 12 mg or pramipexole may be used in non-responders. In patients with RBD and narcolepsy who are on TCAs for narcolepsy, TCAs may be continued with clonazepam added or consider switching to sodium oxybate for cataplexy therapy.

Nightmare disorder is common in children and adolescents and can occur in 4 % of adults. Nightmares can be triggered by either fluoxetine or bupropion use. Dreams can be intensified/enhanced with fluoxetine, bupropion, paroxetine, and citalopram. In patients with nightmares associated with post-traumatic stress disorder (PTSD), prazosin, an α1-adrenergic receptor antagonist, increased TST, increased REM sleep duration, and increased the mean REM duration without altering sleep-onset latency (Taylor et al. 2008). At doses of 0.2–0.6 mg, clonidine, a α_2-adrenergic receptor agonist, is efficacious in treating PTSD-related nightmares. Other medications may be considered for the treatment of PTSD nightmares, but the data are sparse: trazodone, topiramate, atypical antipsychotics, low-dose cortisone, fluvoxamine, triazolam, low-dose cortisol, fluvoxamine, nitrazepam, phenelzine, gabapentin, cyproheptadine, and tricyclic antidepressants. The AASM's clinical practice committee did not recommend the use of either nefazodone or venlafaxine in the treatment of nightmares with PTSD; they had no recommendation regarding clonazepam because of sparse data. Non-pharmacologic therapy (cognitive behavioral therapy, progressive deep muscle relaxation training), hypnosis, eye movement desensitization reprocessing, and the testimony method) may be utilized to treat nightmare disorders (Aurora et al. 2010). For all parasomnias with injurious behavior, environmental safety precautions should be undertaken in tandem with pharmacological measures, good sleep hygiene, regularization of sleep–wake schedule, and avoidance of alcohol intoxication.

7.1 Parasomnias and Plasticity

Normal sleep is a precisely orchestrated symphony of both activation and deactivation of different neuronal systems. Disorders of arousal can arise from dysfunctional and independent activities of different neuronal networks. Single photon emission computed tomography demonstrated significantly increased perfusion in the posterior cingulate cortex and the anterior cerebellum with reduced cerebral blood flow in the fronto-parietal cortices, during a sleepwalking episode, in a 16-year-old man (Bassetti et al. 2000). Deactivation of the prefrontal cortices may explain the amnestic features with somnambulism (Bassetti et al. 2000). Different studies using intracerebral EEG recordings have also demonstrated dissociated wake-like and sleep-like electrocortical activity during sleep (Terzaghi et al. 2009, 2012; Nobili et al. 2011 NeuroImage). TMS studies performed in 8 adult sleepwalkers during wake state showed shorter interval intracortical inhibition, shorter mean cortical silent period, and significant reduction in short latency afferent inhibition when compared to a healthy control group (Oliviero et al. 2007). Concomitant dysfunction of $GABA_A$ and cholinergic pathways may explain both the inability to consolidate slow-wave sleep and the reduced reactivity to sensory stimuli during sleepwalking episodes (Oliviero et al. 2007).

The neurophysiology of RBD remains a puzzle, albeit with clues provided by various investigations. Quantitative EEG recordings in RBD patients showed higher

Φ power in fronto-temporal–occipital regions and lower β power in occipital regions during wakefulness; lower β power was present in the occipital regions during REM sleep (Fantini et al. 2003). Increased delta and theta activities were more marked in the right hemisphere and in central regions compared to occipital regions (Iranzo et al. 2010). More severe EEG slowing was noted in patients who subsequently developed mild cognitive impairment (Iranzo et al. 2010). Increased beta-range cortico-muscle coherence during REM sleep in RBD subjects suggests increased cortical locomotor drive, which may dream enactment behavior (Jung et al. 2012). These findings correlate with increased perfusion in the supplementary motor cortex that was reported during dream enactment behavior in an RBD patient (Dauvilliers et al. 2011). TMS studies using short latency afferent inhibition testing and neuropsychological examination in 10 RBD subjects showed mild cognitive impairment in 6/10 subjects. Mean short latency afferent inhibition in RBD was significantly reduced compared to control subjects and strongly correlated with tests measuring episodic verbal memory and executive functions (Nardone et al. 2012). The above results support dysfunction of the cholinergic system. The same group demonstrated similar results in patients with Parkinson's disease and RBD in another study (Nardone et al. 2012).

Cortical dysfunction manifested by slowing in the quantitative EEG studies may also reflect damage of brainstem structures that regulate REM sleep and activate the neurocortex. In fact, MRI imaging including diffusion tensor imaging and voxel-based morphometric study in 26 idiopathic RBD patients showed significant decreases of fractional anisotropy (a parameter of neuronal fiber integrity) in the tegmentum of the midbrain and rostral pons and increases of mean diffusivity (a parameter of brain tissue integrity) within the pontine reticular formation overlapping with a cluster of decreased fractional anisotropy in the midbrain. Voxel-based morphometry, a measure of gray and white matter volume, revealed increased gray matter densities in both hippocampi (Scherfler et al. 2011).

Abnormal connectivity between cortex and subcortical structures are also invoked. In RBD, blood oxygen-level-dependent functional MRI imaging showed different correlations between the left substantia nigra and the left putamen, between substantia nigra and the right cuneus/precuneus, and between substantia nigra and superior occipital gyrus, when compared with studies in controls and parkinsonian patients. These results suggest altered nigrostriatal and nigrocortical connectivity in RBD, and these findings may predate the onset of obvious motor impairment. These changes in the cuneus/pre-cuneus areas may affect performance of highly integrated tasks including visuospatial imagery, attention, memory retrieval, and self-processing operations. Increased posteromedial cortex connectivity may explain the reduced cognition in RBD patients with respect to attention, memory, and visuospatial changes (Ellmore et al. 2013).

Network analysis of resting-state functional imaging data can show distinct spatial covariance topographies that characterize various neurodegenerative disorders. Parkinson's disease-related covariance pattern (PDRP) is characterized by increases in pallidothalamic, pontine, and cerebellar metabolic activity and by reductions in premotor and parietal association regions. In a cohort of RBD

patients, there was increased PDRP expression in RBD patients. Latent network abnormalities were detected in RBD subjects who had a greater likelihood of subsequent conversion to a progressive neurodegenerative syndrome (Holtbernd et al. 2014).

Abnormalities in various neurotransmitter systems have been invoked in the pathophysiology of RBD, including abnormalities in cholinergic and dopaminergic systems (Kim et al. 2010; Nardone et al. 2012). There is also a hypothesis that RBD is due to a specific degeneration of descending REM-on glutamatergic neurons localized in the caudal sublaterodorsal tegmental nucleus or that of the REM-on GABA/glycinergic premotoneurons localized in the ventral medullary reticular formation (Luppi et al. 2013).

8 Conclusions

Treatment of sleep disorders remains a complex enterprise that is constantly updated based on discoveries that alter our concepts of sleep/wake physiology, sleep disorders pathophysiology, neuroplasticity, neurochemistry, neuroendocrinology, genetics, and pharmacology. Research collaboration with colleagues in other fields may accelerate our understanding of various sleep disorders. Proteomics can identify proteins associated with diseases, which can then be targeted by computer software to design new drugs, whereas genomics offers the potential to treat diseases based upon an individual's specific genetic markers. Understanding the complex processes underlying neuroplasticity may lead to targeted pharmacotherapy and help in the design of drugs that can restore and enhance function among patients with sleep disorders. Drugs that promote synaptic and neuronal plasticity might combat the cognitive dysfunction seen with sleep apnea patients. Biologic agents as well as drugs that target the hypocretin/orexin neuronal systems might help narcoleptic patients. Although current research in nanomedicine is directed toward drug delivery of chemotherapeutic agents, there could be future applications for drug delivery to treat sleep disorders.

References

Alhaider IA, Aleisa AM, Tran T, Alzoubi KH, Alkadhi KA (2010) Chronic caffeine treatment prevents sleep deprivation-induced impairment of cognitive function and synaptic plasticity. Sleep 33:437–444

Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW et al (2014) Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated international restless legs syndrome study group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med 15:860–873. doi:10.1016/j.sleep.2014.03.025 (Epub 17 May 2014)

Altena E, Van Der Werf YD, Sanz-Arigita EJ, Voorn TA, Rombouts SA, Kuijer JP, Van Someren EJ (2008) Prefrontal hypoactivation and recovery in insomnia. Sleep 31:1271–1276

Altena E, Vrenken H, Van Der Werf YD, van den Heuvel OA, Van Someren EJ (2010) Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. Biol Psychiatry 67:182–185

American Academy of Sleep Medicine (2014) International classification of sleep disorders, 3rd edn. American Academy of Sleep Medicine, Darien Il

Anderson S, Vande Griend JP (2014) Quetiapine for insomnia: a review of the literature. Am J Health-Syst Pharm 71:394–402

Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E (2010) Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep 33:1457–1464

Aton SJ, Seibt J, Dumoulin MC, Coleman T, Shiraishi M, Frank MG (2009) The sedating antidepressant trazodone impairs sleep-dependent cortical plasticity. PLoS One 4(7):e6078. doi:10.1371/journal.pone.0006078

Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowduri S, Krippot A et al (2010) Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med 6:389–401

Ayalon L, Ancoli-Israel S, Aka AA, McKenna BS, Drummond SP (2009) Relationship between obstructive sleep apnea severity and brain activation during a sustained attention task. Sleep 32:373–381

Bahammam SA, Sharif MM, Jammah AA, Bahammam AS (2011) Prevalence of thyroid disease in patients with obstructive sleep apnea. Respir Med 105:1755–1760

Barch DM, Carter CS (2005) Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers. Schizophr Res 77:43–58

Barker MG, Greenwood KM, Jakson M, Crowe SF (2005) An evaluation of persisting cognitive effects after withdrawal from long-term benzodiazepine use. J Int Neuropsychol Soc 11:281–289

Barker MJ, Greenwood KM, Jackson M, Crowe SF (2004) Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 18:37–48

Bassetti C, Vella S, Donati F, Wielapp P, Weder B (2000) SPECT during sleep walking. Lancet 356:484–485

Bettica P, Nucci G, Pyke C, Squassante L, Zamuner S, Ratti E, Gomeni R, Alexander R (2012a) Phase I studies on the safety, tolerability, pharmacokinetics and pharmacodynamics of SB-649868, a novel dual orexin receptor antagonist. J Psychopharmacol 26:1058–1070. doi:10.1177/0269881111408954 (Epub 5 Jul 2011)

Bettica P, Squassante L, Groeger JA, Gennery B, Winsky-Sommerer R, Dijk DJ (2012b) Differential effects of a dual orexin receptor antagonist (SB-649868) and zolpidem on sleep initiation and consolidation, SWS, REM sleep, and EEG power spectra in a model of situational insomnia. Neuropsychopharmacology 37:1224–1233

Bettica P, Squassante L, Zamuner S, Nucci G, Danker-Hopfe H, Ratti E (2012c) The orexin antagonist SB-649868 promotes and maintains sleep in men with primary insomnia. Sleep 35:1097–1104

Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A (2001) Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 163:608–613

Black JE, Hirshkowitz M (2005) Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure–treated obstructive sleep apnea/hypopnea syndrome. Sleep 28:464–471

Black JE, Hull SG, Tiller J, Yang R, Harsh JR (2010) The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. J Clin Sleep Med 6:458–466

Bogan R (2014) From bench to bedside: an overview of rotigotine for the treatment of restless legs syndrome. Clin Ther 36:436–455

Bonacci JM, Venci JV, Gandhi MA (2014) Tasimelteon (Hetlioz tm): a New Melatonin receptor agonist for the treatment of Non-24-hour sleep-wake disorder. J Pharm Pract. pii:0897190014544792. Accessed on 16 Sept 2014 (Epub ahead of print)

Borkowska A, Drozdz W, Ziolkowska-Kochan M, Rybakowski J (2007) Enhancing effect of mirtazapine on cognitive functions associated with prefrontal cortex in patients with recurrent depression. Nueropsychopahrmacologia Hung 9:131–136

Boutrel B, Koob GF (2004) What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. Sleep 27:1181–1194

Boyle J, Wolford D, Gargano C, McCrea J, Cummings C, Cerchio K, Lines C (2009) Next day residual effects of Gaboxadol and flurazepam administered at bedtime: a randomized double-blind study in healthy elderly subjects. Hum Psychopharmacol 24:61–71

Braver HM, Block AJ (1994) Effect of nasal spray, positional therapy, and the combination thereof in the asymptomatic snorer. Sleep 17:516–521

Brouillette RT, Manoukian JJ, Ducharme FM et al (2001) Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr 138:838–844

Buysse DJ (2011) Clinical pharmacology of other drugs used as hypnotics. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. Elsevier Saunders, Missouri

Campana L, Eckert DJ, Patel SR, Malhotra A (2010) Pathophysiology and genetics of obstructive sleep apnea. Indian J Med Res 131:176–187

Canova CR, Downs SH, Knoblauch A et al (2004) Increased prevalence of perennial allergic rhinitis in patients with obstructive sleep apnea. Respiration 71:138–143

Carter LP, Griffiths RR, Mintzer MZ (2009) Cognitive, psychomotor, and subjective effects of sodium oxybate and triazolam in healthy volunteers. Psychopharmacology (Berl) 206:141–154. doi:10.1007/s00213-009-1589-1 (Epub 20 Jun 2009)

Castren E, Hen R (2013) Neuronal plasticity and antidepressant actions. Trends Neurosci 36:259–267

Chan KC, Shi L, So HK, Wang D, Liew AW, Rasalkar DD et al (2014) Neurocognitive dysfunction and grey matter density deficit in children with obstructive sleep apnoea. Sleep Med 15:1055–1061. doi:10.1016/j.sleep.2014.04.011 (Epub 6 Jun 2014)

Civardi C, Naldi P, Cantello R (2004) Cortico-motoneurone excitability in patients with obstructive sleep apnoea. J Sleep Res 13:159–163

Civardi C, Collini A, Monaco F, Cantello R (2009) Applications of transcranial magnetic stimulation in sleep medicine. Sleep Med Rev 13:35–46

Cohrs S, Rodenbeck A, Guan Z, Pohlmann K, Jordan W, Meier A, Ruther E (2004) Sleep promoting properties of quetiapine in healthy subjects. Psychopharmacology (Berl) 174:421–429

Cooper DC, Moore SJ, Staff NP, Spruston N (2003) Psychostimulant-induced plasticity of intrinsic neuronal excitability in ventral subiculum. J Neurosci 23:9937–9946

Coull JT, Buchel C, Friston KJ, Frith CD (1999) Noradrenergically mediated plasticity in a human attentional neuronal network. NeuroImage 10:705–715

Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ et al (2011) Harnessing neuroplasticity for clinical applications. Brain 134:1591–1609

Da Silveira CKB, Furini CRG, Benetti F, da Cruz Monteiro S, Izquierdo I (2013) The role of histamine receptors in the consolidation of object recognition memory. Neurobiol Lear Mem 103:64–71

Dagytė G, Trentani A, Postema F, Luiten P, Den Boer J, Johan A et al (2010) The novel antidepressant agomelatine normalizes hippocampal neuronal activity and promotes neurogenesis in chronically stressed rats. CNS Neurosci Ther 16:195–207

Dang-Vu TT (2013) Neuroimaging findings in narcolepsy with cataplexy. Curr Neurol Neurosci Rep 13:349–356

Das A, Anupa AV, Radhakrishnan A (2013) Reduced plastic brain responses to repetitive transcranial magnetic stimulation in severe obstructive sleep apnea syndrome. Sleep Med 14:636–640. doi:10.1016/j.sleep.2013.04.008 (Epub 2013 Jun 7)

Dauvilliers Y, Bassetti C. Lammers GJ, Arnulf I, Mayer Geert, Rodenbeck A et al (2013) HARMONY I study group. www.thelancet.com/neurology, vol 12. Accessed 11 Sept 2014

Dauvilliers Y, Yves D, Boudousq V, Vincent B, Lopez R, Regis L et al (2011) Increased perfusion in supplementary motor area during a REM sleep behaviour episode. Sleep Med 12:531–532

Davies CH, Starkey SJ, Pozza MF, Collingridge GL (1991) GABA autoreceptors regulate the induction of LTP. Nature 349:609–611

Dayat E, Serpero L, Kheirandish-Gozal L et al (2009) Leukotriene pathways and in vitro adenotonsillar cell proliferation in children with obstructive sleep apnea. Chest 135:1142–1149

Deacon S, Staner L, Staner C et al (2007) Effect of short-term treatment with Gaboxadol on sleep maintenance and initiation in patients with primary insomnia. Sleep 30:281–287

Diana M, Mereu G, Mura A, Fadda F, Passino N, Gessa G (1991) Low doses of gamma-hydroxybutyric acid stimulate the firing rate of dopaminergic neurons in unanesthetized rats. Brain Res 566:208–211

Dostal M, Weber-Schoendorfer C, Sobesky J, Schaefer C (2012) Pregnancy outcome following use of levodopa, pramipexole, ropinirole, and rotigotine for rest- less legs syndrome during pregnancy: a case series. Eur J Neurol 20:1241e6

Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC et al (2014) Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom Disease). Sleep Med. pii:S1389-9457(14)00237-8. doi:10.1016/j.sleep.2014.05.009. (Epub ahead of print) Review

Ellmore TM, Castriotta RJ, Hendley KL, Aalbers BM, Furr-Stimming E, Hood AJ et al (2013) Altered nigrostriatal and nigrocortical functional connectivity in rapid eye movement sleep behavior disorder. Sleep 36:1885–1892. doi:10.5665/sleep.3222

Entezari-Taher M, Singleton JR, Jones CR, Meekins G, Petajan JH, Smith AG (1999) Changes in excitability of motor cortical circuitry in primary restless legs syndrome. Neurology 53:1201–1205

Espana RA, Scammell TE (2004) Sleep neurobiology for the clinician. SLEEP 27:811–820

Fantini ML, Gagnon JF, Petit D, Rompré S, Décary A, Carrier J et al (2003) Slowing of electroencephalogram in rapid eye movement sleep behavior disorder. Ann Neurol 53:774–780

FDA Peripheral and Central Nervous System Advisory Committee May 22 (2013) Suvorexant background information. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM352969. Accessed on 07 Sept 2014

Fields RB, Van Kammen DP, Peters JL, Rosen J, Van Kammen WB, Nugent A (1988) Clonidine improves memory function in schizophrenia independently from change in psychosis. Preliminary findings. Schizophr Res 1:417–423

Finnimore AJ, Roebuck M, Sajkov D et al (1995) The effects of the GABA agonist, baclofen, on sleep and breathing. Eur Respir J 8:230–234

France CP, Weltman RH, Koek W et al (2006) Acute and chronic effects of ramelteon in rhesus monkeys (Macaca mulatta): dependence liability studies. Behav Neurosci 120:535–541

Fresnoza S, Stiksrud E, Klinker F, Liebetanz D, Paulus W, Kuo MF, Nitsche MA (2014) Dosage-dependent effect of dopamine D2 receptor activation on motor cortex plasticity in humans. J Neurosci 34:10701–10709

Fuller PM, Saper CB, Lu J (2007) The pontine REM switch: past and present. J Physiol 584:735–741

Gallopin T, Fort P, Eggermann E et al (2000) Identification of sleep-promoting neurons in vitro. Nature 404:992–995

Gao XB (2012) Plasticity in neurons synthesizing wake/arousal promoting hormone hypocretin/orexin. Vitam Horm 89:35–59

Gao XB, Wang AH (2010) Experience-dependent plasticity in hypocretin/orexin neurons: re-setting the arousal threshold. Acta Physiol (Oxf) 198:251–262

Gao B, Kilic E, Baumann C, Hermann DM, Bassetti CL (2008) Gamma-hydroxybutyrate accelerates functional recovery after focal cerebral ischemia. Cerebrovascular Dis 26:413–419

García-Borreguero D, Allen RP, Kohnen R, Högl B, Trenkwalder C, Oertel W, Hening WA, Paulus W, Rye D, Walters A, Winkelmann J, Earley CJ; International Restless Legs Syndrome Study Group (2007) Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a world association of sleep medicine-international restless legs syndrome study group consensus conference at the max planck institute. Sleep Med 8:520–530. Epub 2007 Jun 1. Erratum in: Sleep Med 8(7–8):788

Gianlorenco AC, Serafim KR, Canto-de-Souza A, Mattioli R (2012) Emotional memory consolidation impairment induced by histamine is mediated by H1 but not H2 receptors. Brain Res Bull 89:197–202

Gorsler A, Liepert J (2007) Influence of cabergoline on motor excitability in patients with restless legs syndrome. J Clin Neurophysiol 24:456–460

Grace KP, Hughes SW, Shahabi S, Horner RL (2013) K+ channel modulation causes genioglossus inhibition in REM sleep and is a strategy for reactivation. Respir Physiol Neurobiol 188:277–288. doi:10.1016/j.resp.2013.07.011 (Epub 18 Jul 2013). Review

Grace KP, Hughes SW2, Horner RL3 (2014) Identification of a pharmacological target for genioglossus reactivation throughout sleep. Sleep 37:41–50. doi:10.5665/sleep.3304

Guilleminault C, Hayes B (1983) Naloxone, theophylline, bromocriptine, and obstructive sleep apnea. Negative results. Bull Eur Physiopathol Respir 19:632–634

Guilleminault C, Philip P (1996) Tiredness and somnolence despite initial treatment of obstructive sleep apnea syndrome (what to do when an OSAS patient stays hypersomnolent despite treatment). Sleep 19(9 Suppl):S117–22

Guilleminault C, Abad VC (2009) Narcolepsy. In: Chokroverty S (ed) Sleep disorders medicine: basic science, technical considerations, and clinical aspects, 3rd edn. Saunders Elsevier, Philadelphia

Gündüz A, Adatepe NU, Kiziltan ME, Karadeniz D, Uysal O (2012) Cırcadian changes in cortical excitability in restless legs syndrome. J Neurol Sci 316:122–125. doi:10.1016/j.jns.2012.01.008 (Epub 2 Feb 2012)

Hallam KT, Olver JS, McGrath C, Norman TR (2003) Comparative cognitive and psychomotor effects of single doses of Valeriana officianalis and triazolam in healthy volunteers. Hum Psychopharmacol 18:619–625

Hanzel DA, Proia NG, Hudgel DW (1991) Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest 100:416–421

Havekes R, Vecsey C, Abel T (2012) The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. Cell Signal 24:1251–1260

Hedner J, Kraiczi H, Peker Y (2003) Reduction of sleep-disordered breathing after physostigmine. Am J Respir Crit Care Med 168:1246–1251

Hefti K, Host SC, Sovago J, Bachmann V, Buck A, Ametamey SM et al (2013) Increased metabotropic glutamate receptor subtype 5 availability in human brain after one night without sleep. Bio Psychiatry 73:161–168

Heidegger T, Krakow K, Ziermann U (2010) Effects of antiepileptic drugs on associative LTP-like plasticity in human motor cortex. Eur J Neurosci 32:1215–1222

Hening WA, Allen PR, Walters AS, Chokroverty S (2009) Motor functions and dysfunctions of sleep. In: Chokroverty S (ed) Sleep disorders medicine: basic science, technical considerations, and clinical aspects. Saunders Elsevier, Philadelphia, PA

Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K, Lines C, Roth T, Michelson D et al (2012) Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology 79:2265–2274. doi:10.1212/WNL.0b013e31827688ee (Epub 28 Nov 2012)

Herrmann BL, Wessendorf TE, Ajaj W et al (2004) Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly. Eur J Endocrinol 151:309–315

Hirai K, Kita M, Ohta H, Nishikawa H, Fujiwara Y, Ohkawa S, Miyamoto M (2005) Ramelteon (TAK-375) accelerates reentrainment of circadian rhythm after a phase advance of the light-dark cycle in rats. J Biol Rhythms 20:27–37

Högl B, Oertel WH, Stiasny-Kolster K, Geisler P, Beneš H, García-Borreguero D, Trenkwalder C, Poewe W, Schollmayer E, Kohnen R (2010) Treatment of moderate to severe restless legs syndrome: 2-year safety and efficacy of rotigotine transdermal patch. BMC Neurol 10:86

Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A et al (2014) Abnormal metabolic network activity in REM sleep behavior disorder. Neurology 82:620–627. doi:10.1212/WNL.0000000000000130 (Epub 22 Jan 2014)

Hübner A, Krafft A, Gadient S, Werth E, Zimmermann R, Bassetti CL (2013) Characteristics and determinants of restless legs syndrome in pregnancy: a prospective study. Neurology 80:738–742. doi:10.1212/WNL.0b013e318283baf3 (Epub 6 Feb 2013)

Hurault-Delarue C, Montastruc JL, Beau AB, Lacroix I, Damase-Michel C (2014) Pregnancy outcome in women exposed to dopamine agonists during pregnancy: a pharmacoepidemiology study in EFEMERIS database. Arch Gynecol Obstet 290:263–270. doi:10.1007/s00404-014-3210-z (Epub 25 Mar 2014)

Huynh NT, Prilipko O, Kushida CA, Guilleminault C (2014) Volumetric Brain Morphometry Changes in Patients with Obstructive Sleep Apnea Syndrome: Effects of CPAP Treatment and Literature Review. Front Neurol 5:58. doi:10.3389/fneur.2014.00058. eCollection 2014. Accessed on 12 Sept 2014

Inocente C, Arnulf I, Bastuji H, Thibault-Stoll A, Raoux A, Reimão R et al (2012) Pitolisant, an inverse agonist of the histamine H3 receptor: an alternative stimulant for narcolepsy-cataplexy in teenagers with refractory sleepiness. Clin Neuropharmacol 352:55–60

Inoue Y, Takata K, Sakamoto I et al (1999) Clinical efficacy and indication of acetazolamide treatment on sleep apnea syndrome. Psychiatry Clin Neurosci 53:321–322

Iranzo A, Isetta V, Molinuevo JL, Serradell M, Navajas D, Farre R et al (2010) Electroencephalographic slowing heralds mild cognitive impairment in idiopathic REM sleep behavior disorder. Sleep Med 11:534–539. doi:10.1016/j.sleep.2010.03.006 (Epub 11 May 2010)

Jha A, Sharma SK, Tandon N, Lakshmy R, Kadhiravan T, Handa KK, Gupta R, Pandey RM, Chaturvedi PK (2006) Thyroxine replacement therapy reverses sleep-disordered breathing in patients with primary hypothyroidism. Sleep Med 7:55–61

Johnsa JD, Neville MW (2014) Tasimelteon: a melatonin receptor agonist for Non-24 sleep-wake disorder. Ann Pharmacother. pii: 1060028014550476. (Epub ahead of print). Accessed 17 Sept 2014

Joo EY, Hong SB, Han SJ, Suh M (2011) Suppression of motor evoked potential during cataplexy. Sleep Med 12:306–307

Joo EY, Hong SB, Kim HJ, Lim YH, Koo DL, Ji KH, Tae WS (2010) The effect of modafinil on cortical excitability in patients with narcolepsy: a randomized, placebo- controlled crossover study. Sleep Med 11:862–869

Juan WS, Huang SY, Chang CC, Hung YC, Lin YW, Chen TY et al (2013) Melatonin improves neuroplasticity by upregulating the growth-associated protein-43 (GAP-43) and NMDAR postsynaptic density-95 (PSD-95 proteinsin cultured neurons exposed to glutamate excitotoxicity and in rats subjected to transient focal cerebral ischemia even during a long-term recovery period. J Pineal Res. doi:10/111/jpi.12114. Accessed 3 Sept 2014

Jung KY, Cho JH, Ko D, Seok HY, Yoon HK, Lee HJ et al (2012) Increased corticomuscular coherence in idiopathic REM sleep behavior disorder. Front Neurol 3:60. PubMed PMID: 2253619

Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Cotreau MM, Harmatz JS, Shader RI (1997) Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. J Clin Pharmacol 37:693–703

Karim A, Tolbert D, Cao C (2006) Disposition kinetics and tolerance of escalating single doses of ramelteon, a high affinity MT_1 and MT_2 melatonin receptor agonist indicated for treatment of insomnia. J Clin Pharmacol 46:140–148

Keefe DL, Watson R, Naftolin F (1999) Hormone replacement therapy may alleviate sleep apnea in menopausal women: a pilot study. Menopause 6:196–200

Khan A, Harrison SL, Kezirian EJ, Ancoli-Israel S, O'Hearn D, Orwoll E et al (2013) Osteoporotic fractures in men (MrOS) study research group. Obstructive sleep apnea during rapid eye movement sleep, daytime sleepiness, and quality of life in older men in osteoporotic fractures in men (MrOS) sleep study. J Clin Sleep Med 9:191–198. doi:10.5664/jcsm.2474

Kheirandish L, Goldbart AD, Gozal D (2006) Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. Pediatrics 117:e61–e66

Kheirandish-Gozal L, Yoder K, Kulkarni R, Gozal D, Decety J (2014) Preliminary functional MRI neural correlates of executive functioning and empathy in children with obstructive sleep apnea. Sleep 37:587–592. doi:10.5665/sleep.3504

Kiely JL, Nolan P, Mchicholas WT (2004) Intranasal corticosteroid therapy for obstructive sleep apnea in patients with co-existing rhinitis. Thorax 59:50–55

Kim YK, Yoon IY, Kim JM, Jeong SH, Kim KW, Shin YK et al (2010) The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. Eur J Neurol 17:487–492. doi:10.1111/j.1468-1331.2009.02854.x (Epub 24 Nov 2009)

Kohler CA, da Silva WC, Benetti F, Bonini JS (2011) Histaminergic mechanisms for modulation of memory systems. Neural Plasticity Article ID 328602, 16 pages. doi:10.1.1155/2011/328602. Accessed on 29 Aug 2014

Koo BB, Patel SR, Strohl K, Hoffstein V (2008) Rapid eye movement-related sleep-disordered breathing: influence of age and gender. Chest 134:1156–1161. doi:10.1378/chest.08-1311 (Epub 23 Sept 2008)

Kraiczi H, Hedner J, Dahlof P et al (1999) Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. Sleep 22:61–67

Kume A (2014) Gabapentin enacarbil for the treatment of moderate to severe primary restless legs syndrome (Willis-Ekbom disease): 600 or 1,200 mg dose? Neuropsychiatric Disease Treatment 10:249–262

Kutukcu Y, Dogruer E, Yetkin S, Ozgen F, Vural O, Aydin H (2006) Evaluation of periodic leg movements and associated transcranial magnetic stimulation parameters in restless legs syndrome. Muscle Nerve 33:133–137

Lam SP, Fong SY, Ho CK, Yu MW, Wing YK (2008) Parasomnia among psychiatric outpatients: clinical, epidemiologic, cross-sectional study. J Clin Psychiatry 69:1374–1382

Lanza G. Lanza G, Cantone M, Lanuzza B, Pennisi M, Bella R, Pennisi G, Ferri R (2014) Distinctive patterns of cortical excitability to transcranial magnetic stimulation in obstructive sleep apnea syndrome, restless legs syndrome, insomnia, and sleep deprivation. Sleep Med Rev pii: S1087-0792(14)00042-2. doi:10.1016/j.smrv.2014.04.001 (Epub ahead of print); downloaded 09-14-14

LaPorte E, Sarris J, Stough C, Scholey A (2011) Neurocognitive effects of kava (Piper methysticum): a systematic review. Hum Psychopharmacol 26:102–111. doi:10.1002/hup.1180 (Epub 16 Mar 2011)

Lazewska D, Kiec-Konowicz K (2010) Recent Advances in histamine H3 receptor antagonists/inverse agonists. Expert Opin Ther Pat 20:1147–1169

Lee DO, Ziman RB, Perkins AT, Poceta JS, Walters AS, Barrett RW (2011) XP053 Study Group. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J Clin Sleep Med 7:282–292

Leu-Semenescu S, Nittur N, Golmard JL, Arnulf I (2014) Effects of pitolisant, a histamine H3 inverse agonist, in drug-resistant idiopathic and symptomatic hypersomnia: a chart review. Sleep Med 15:681–687

Lin CC, Tsan KW, Chen PJ (1992) The relationship between sleep apnea syndrome and hypothyroidism. Chest 102(6):1663–1667

Lin JS, Sergeeva OA, Haas HL (2011) Histamine H3 receptors and sleep-wake regulation. J Pharmacol Exp Ther 336:17–23

Liu PY, Yee B, Wishart SM et al (2003) The short-term effects of high- dose testosterone on sleep, breathing, and function in older men. J Clin Endocrinol Metab 88:3605–3613
Lu Z, Tang X, Huang X (1998) Phrenic nerve conduction and diaphragmatic motor evoked potentials: evaluation of respiratory dysfunction. Chin Med J (Engl) 111:496–499
Lucassen PJ, Meerlo P, Naylor AS, Van Dam AM, Dayer AG, Fuchs E, Oomen CA, Czeh B (2010) Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: implications for depression and antidepressant action. Eur Neuropsychopharmacol 20:1–17
Luppi PH, Clément O, Valencia Garcia S, Brischoux F, Fort P (2013) New aspects in the pathophysiology of rapid eye movement sleep behavior disorder: the potential role of glutamate, gamma-aminobutyric acid, and glycine. Sleep Med 14:714–718. doi:10.1016/j.sleep.2013.02.004 (Epub 19 Jun 2013)
Maffei A (2011) The many forms and functions of long-term plasticity at GABAergic synapses. Neural Plast 254724. Accessed 20 Aug 2014
Mair RG, McEntee WJ (1986) Cognitive enhancement in Korsakoff's psychosis by clonidine: a comparison with L-dopa and ephedrine. Psychopharmacol (Berl) 88:374–380
Mamelak M (2007) Alzheimer's disease, oxidative stress and gammahydroxybutyrate. Neurobiol Aging 28:1340–1360 (Epub 11 Jul 2006)
Manber R, Kuo TF, Cataldo N et al (2003) The effects of hormone re placement therapy on sleep-disordered breathing in postmenopausal women: a pilot study. Sleep 26:163–168
Marín-Burgin A, Schinder AF (2012) Requirement of adult-born neurons for hippocampus-dependent learning. Behav Brain Res 227:391–399. doi:10.1016/j.bbr.2011.07.001 (Epub 7 Jul 2011)
Marshall NS, Yee BJ, Desai AV et al (2008) Two randomized placebo- controlled trials to evaluate the efficacy and tolerability of mirtazapine for the treatment of obstructive sleep apnea. Sleep 31:824–831
Mattay VS, Callicott JH, Bertolino A, Heaton I, Frank JA, Coppola R et al (2000) Effects of dextroamphetamine on cognitive performance and cortical activation. Neuroimage 12:268–275
Meisenzahl EM, Scheuerecker J, Zipse M, Ufer S, Wiesmann M, Frodl T et al (2006) Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. Eur Arch Psychiatry Clin Neurosci 256:522–531 (Epub 6 Dec 2006)
Melo-Silva CA, Borel JC, Gakwaya S, Sériès F (2013) Acute upper airway muscle and inspiratory flow responses to transcranial magnetic stimulation during sleep in apnoeic patients. Exp Physiol 98:946–956. doi:10.1113/expphysiol.2012.070359 (Epub 7 Dec 2012)
Mets MA, De Vries JM, de Senerpont Domis LM, Volkerts ER,Olivier B, Verster JC (2011) Next-day effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on highwaydriving performance, memory functioning, psychomotor performance and mood in healthy adult subjects.Sleep 34:1327–1334
Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J et al (2014) Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 13:461–471. doi:10.1016/S1474-4422(14)70053-5 (Epub 27 Mar 2014)
Mindell JA, Emslie G, Blumer J et al (2006) Pharmacologic management of insomnia in children and adolescents: consensus statement. Pediatrics 117:e1223
Morgenthaler T, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN et al (2007) Standards of Practice committee of the American academy of sleep medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 3012:1705–1711. Review
Morgenthaler T, Kramer M, Alessi C et al (2006) American academy of sleep medicine. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American academy of sleep medicine report. Sleep 29:1415–1419
Nagane A, Baba H, Nakano Y, Maeshima H, Hukatsu M, Ozawa K et al (2014) Comparative study of cognitive impairment between medicated and medication-free patients with remitted major depression: Class-specific influence by tricyclic antidepressants and newer antidepressants.

Psychiatry Res 218:101–105. Available online 16 April 2014 at www.elsevier.com/locate/psychres. Accessed on 06 Sept 2014

Nakanishi S et al (2014) Distinct dopaminergic control of the direct and indirect pathways in reward-based and avoidance learning behaviors. Neuroscience http://dx.doi.org/10.1016/j.neuroscience.2014.04.026. Accessed 13 Sept 2014

Nardone R, Ausserer H, Bratti A, Covi M, Lochner P, Marth R, Tezzon F (2006) Cabergoline reverses cortical hyperexcitability in patients with restless legs syndrome. Acta Neurol Scand 114:244–249

Nardone R, Bergmann J, Brigo F, Christova M, Kunz A, Seidl M et al (2013a) Functional evaluation of central cholinergic circuits in patients with Parkinson's disease and REM sleep behavior disorder: a TMS study. J Neural Transm 120:413–422. doi:10.1007/s00702-012-0888-6 (Epub 19 Aug 2012)

Nardone R, Bergmann J, Kunz A, Christova M, Brigo F, Tezzon F et al (2012) Cortical afferent inhibition is reduced in patients with idiopathic REM sleep behavior disorder and cognitive impairment: a TMS study. Sleep Med 13:919–925. doi:10.1016/j.sleep.2012.03.009 (Epub 21 Jun 2012)

Nardone R, Höller Y, Brigo F, Tezzon F, Golaszewski S, Trinka E (2013b) Transcranial magnetic stimulation and sleep disorders: pathophysiologic insights. Sleep Med 14:1047–1058. doi:10.1016/j.sleep.2013.04.025 (Epub 3 Aug 2013). Review

Nitsche MA, Müller-Dahlhaus F, Paulus W, Ziemann U (2012) The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. J Physiol 590(Pt 19):4641–4662. doi:10.1113/jphysiol.2012.232975 (Epub 6 Aug 2012). Review

Nobili L, Ferrara M, Moroni F, De Gennaro L, Russo GL, Campus C et al (2011) Dissociated wake-like and sleep-like electro-cortical activity during sleep. Neuroimage 58:612–619. doi:10.1016/j.neuroimage.2011.06.032 (Epub 21 Jun 2011)

Ohayon MM, Guilleminault C, Priest RG (1999) Night terror, sleepwalking, and confusional arousals in the general population: their frequency and relationship to other sleep and mental disorders. J Clin Psychiatry 60:268–276

Olde Rikkert MG, Rigaud AS (2001) Melatonin in elderly patients with insomnia. A systematic review. Z Gerontol Geriatr 34:491–497

Oliviero A, Della Marca G, Tonali PA, Pilato F, Saturno E, Dileone M et al (2007) Functional involvement of cerebral cortex in adult sleepwalking. J Neurol 254:1066–1072 (Epub 12 Mar 2007)

Opie GM, Catcheside PG, Usmani ZA, Ridding MC, Semmler JG (2013) Motor cortex plasticity induced by theta burst stimulation is impaired in patients with obstructive sleep apnoea. Eur J Neurosci 37:1844–1852. doi:10.1111/ejn.12203 (Epub 7 Apr 2013)

Oranje B, Glenthoj B (2013) Clonidine normalizes sensori-motor gating deficits in patients with schizophrenia on stable medication. Schizophr Bull 39:684–691

Owens JA, Mindell JA (2011) Pediatric insomnia. Pediatr Clin North Am 58:555–569

Owens JA (2009) Pharmacotherapy of pediatric insomnia. J Am Acad Child Adolesc Psychiatry 48:99–107

Park SW, Lee CH, Cho HY, Seo MK, Lee JG, Lee BJ et al (2013) Effects of antipsychotic drugs on the expression of synaptic proteins and dendritic outgrowth in hippocampal neuronal cultures. Synapse 67:224–234. doi:10.1002/syn.21634

Pawlik MT, Hansen E, Waldhauser D et al (2005) Clonidine premedication in patients with sleep apnea syndrome: a randomized, double- blind, placebo-controlled study. Anesth Analg 101:1374–1380

Pedraza C, García FB, Navarro JF (2009) Neurotoxic effects induced by gammahydroxybutyric acid (GHB) in male rats. Int J Neuropsychopharmacol 12:1165–1177. doi:10.1017/S1461145709000157 (Epub 17 Mar 2009)

Pickett CK, Regensteiner JG, Woodard WD et al (1989) Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. J Appl Physiol 66:1656–1661

Pietrzak RH, Mollica CM, Maruff P, Snyder PJ (2006) Cognitive effects of immediate-release methylphenidate in children with attention-deficit /hyperactivity disorder. Neurosci Biobehav Rev 30:1225–1245

Pilar-Cuéllar F, Vidal R, Díaz A, Castro E, dos Anjos S, Pascual-Brazo J et al (2013) Neural plasticity and proliferation in the generation of antidepressant effects: hippocampal implication. Neural Plast 2013:537265. doi:10.1155/2013/537265 (Epub 19 Jun 2013). Accessed on 14 Sept 2014

Poe GR, Walsh CM, Bjorness TE (2010) Cognitive neuroscience of sleep. Prog Brain Res 185:1–19

Prilipko O, Huynh N, Thomason ME, Kushida CA, Guilleminault C (2014) An fMRI study of cerebrovascular reactivity and perfusion in obstructive sleep apnea patients before and after CPAP treatment. Sleep Med 15:892–898. doi:10.1016/j.sleep.2014.04.004 (Epub 4 May 2014)

Puustinen J, Lahteenmaki R, Polo-Kantola P, Saio P, Vahlberg T, Lyles A et al (2014) Effect of withdrawal from long-term use of temazepam, zopiclone or zolpidem as hypnotic agents on cognition in older adults. Eur J Clin Pharmacol 70:319–329

Quatrale R, Manconi M, Gastaldo E, Eleopra R, Tugnoli V, Tola MR et al (2003) Neurophysiological study of corticomotor pathways in restless legs syndrome. Clin Neurophysiol 114:1638–1645

Quera-Salva MA, Lemoine P, Guilleminault C (2010) Impact of the novel antidepressant agomelatine on disturbed sleep-wake cycles in depressed patients. Hum Psychopharmacol 25:222–229

Rajaratnam S, Cohen D, Rogers N (2009a) Melatonin and melatonin analogues. Sleep Med Clin 4:179–193

Rajaratnam SM, Polymeropoulos MH, Fisher DM, Roth T, Scott C, Birznieks G, Klerman EB (2009b) Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. Lancet 373:482–491. doi:10.1016/S0140-6736(08)61812-7

Reske M, Eidt CA, Delis DC, Paulus MP (2010) Nondependent stimulant users of cocaine and prescription amphetamines show verbal learning and memory deficits. Biol Psychiatry 68:762–769

Resta O, Carratù P, Carpagnano GE, Maniscalco M, Di Gioia G, Lacedonia D, Giorgino R, De Pergola G (2005) Influence of subclinical hypothyroidism and T4 treatment on the prevalence and severity of obstructive sleep apnoea syndrome (OSAS). J Endocrinol Invest 28:893–898

Riekkinen M, Riekkinen P Jr (1999) Alpha$_2$-adrenergic agonist clonidine for improving spatial working memory in Parkinson's disease. J Clin Psychopharmacol 19:444–449

Rizzo V, Aricò I, Liotta G, Ricciardi L, Mastroeni C, Morgante F et al (2010) Impairment of sensory-motor integration in patients affected by RLS. J Neurol 257:1979–1985. doi:10.1007/s00415-010-5644-y (Epub 16 Jul 2010)

Rizzo V, Arico I, Mastroeni C, Morgante F, Liotta G, Girlanda P, Silvestri R, Quartarone A (2009) Dopamine agonists restore cortical plasticity in patients with idiopathic restless legs syndrome. Mov Disord 24:710–715

Rosler KM, Nirkko AC, Rihs F, Hess CW (1994) Motor-evoked responses to transcranial brain stimulation persist during cataplexy: a case report. Sleep 17:168–171

Roth T, Rogowski R, Hull S, Schwartz H, Koshorek G, Corser B, Seiden D (2007) Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep 30:1555–1561

Roth T, White D, Schmidt-Nowara W et al (2006) Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP- adherent adults. Clin Ther 28:689–706

Sakellaropoulou AV, Hatzistilianou MN, Emporiadou MN, Aivazis VT, Rousso I, Athanasiadou-Piperopoulou F (2011) Evaluation of thyroid gland function in children with obstructive apnea hypopnea syndrome. Int J Immunopathol Pharmacol 24:377–386

Saletin JM, Walker MP (2012) Nocturnal mnemonics: sleep and hippocampal memory processing. Front Neurol 3:59

Saletu M, Anderer P, Saletu-Zyhlarz GM, Mandl M, Saletu B, Zeithofer J (2009) Modafinil improves information processing speed and increases energetic resources for orientation of attention in narcoleptics: double-blind placebo-controlled ERP studies with low-resolution brain electromagnetic tomography (LORETA). Sleep Med 10:850–858. doi:10.1016/j.sleep.2008.12.005 (Epub 1 Apr 2009)

Saletu-Zvhlarz G, Anderer P, Gruber G (2003) Insomnia related to post- menopausal syndrome and hormone replacement therapy: sleep laboratory studies on baseline differences between patients and controls and double-blind, placebo-controlled investigations on the effects of a novel estrogen-progestogen combination (Climodien, Lafamme) versus estrogen alone. J Sleep Res 12:239–254

Santarnecchi E, Sicilia I, Richiardi J, Vatti G, Polizzotto NR, Marino D et al (2013) Altered cortical and subcortical local coherence in obstructive sleep apnea: a functional magnetic resonance imaging study. J Sleep Res 22:337–347. doi:10.1111/jsr.12006 (Epub 21 Nov 2012)

Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. Nature 437:1257–1263

Sasada K, Iwamoto K, Kawano N, Kohmura K, Yamamoto M, Aleksic B et al (2013) Effects of repeated dosing with mirtazapine, trazodone, or placebo on driving performance and cognitive function in healthy volunteers. Hum Psychopharmacol 28(3):281–286. doi:10.1002/hup.2321 (Epub 10 May 2013)

Scalise A, Cadore IP, Gigli GL (2004) Motor cortex excitability in restless legs syndrome. Sleep Med 5:393–396

Scalise A, Pittaro-Cadore I, Golob EJ, Gigli GL (2006) Absence of postexercise and delayed facilitation of motor cortex excitability in restless legs syndrome: evidence of altered cortical plasticity? Sleep 29:770–775

Scalise A, Pittaro-Cadore I, Janes F, Marinig R, Gigli GL (2010) Changes of cortical excitability after dopaminergic treatment in restless legs syndrome. Sleep Med 11:75–81. doi:10.1016/j.sleep.2009.05.003

Scammell TE, Winrow CJ (2011) Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol 51:243–266

Scherfler C, Frauscher B, Schocke M, Iranzo A, Gschliesser V, Seppi K et al (2011) White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. Ann Neurol 69:400–407. doi:10.1002/ana.22245 (Epub 28 Dec 2010)

Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M (2008) Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 4:487–504

Schwartz JC (2011) The histamine H3 receptor: from discovery to clinical trials with pitolisant. Br J Pharmacol 163:713–721

Seibt J, Aton SJ, Jha SK, Coleman T, Dumoulin MC, Frank MG (2008) The non-benzodiazepine hypnotic zolpidem impairs sleep-dependent cortical plasticity. Sleep 31:1381–1391

Serafini A, Lorenzut S, Gigli GL, Merlino G, Valente M (2010) The use of rotigotine in the treatment of restless legs syndrome. Ther Adv Neurol Disord 3:241–248

Sériès F, Wang W, Similowski T (2009) Corticomotor control of the genioglossus in awake OSAS patients: a transcranial magnetic stimulation study. Respir Res 10:74. doi:10.1186/1465-9921-10-74

Shepherd JD (2012) Memory, plasticity and sleep—a role for calcium permeable AMPA receptors? Front Mol Neurosci 5:49

Silver N, Allen RP, Senerth J, Earley CJ (2011) A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 12:440–444 Epub 2011 Jan 15

Sircar R, Wu LC, Reddy K, Sircar D, Basak AK (2011) GHB-Induced cognitive deficits during adolescence and the role of NMDA receptor. Curr Neuropharmacol 9:240–243. doi:10.2174/157015911795017038

Smit HJ, Rogers PJ (2000) Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. Psychopharmacology 152:167–173

Smith PL, Haponik EF, Allen RP et al (1983) The effects of protriptyline in sleep-disordered breathing. Am Rev Respir Dis 127:8–13
Snead OC 3rd, Gibson KM (2005) Gamma-hydroxybutyric acid. N Engl J Med 352:2721–2732
Srivanitchapoom P, Pandey S2, Hallett M (2014) Restless legs syndrome and pregnancy: a review. Parkinsonism Relat Disord 20:716–722
Stahl SM (2008) Selective histamine H1 antagonism: novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. CNS Spectr 13:1027–1038
Stenberg JH, Terevnikov V, Joffe M, Tiihonen J, Tchoukhine E, Burkin M, Joffe G (2010) Effects of add-on mirtazapine on neurocognition in schizophrenia: a double-blind, randomized, placebo-controlled study. Int J Neuropsychopharmacol 13:433–441
Stewart DA, Grunstein RR, Barthon-Jones M (1992) Androgen blockade does not affect sleep-disordered breathing or chemosensitivity in men with obstructive sleep apnea. Am Rev Respir Dis 146:1389–1393
Stiasny-Kolster K, Haeske H, Tergau F, Müller HH, Braune HJ, Oertel WH (2003) Cortical silent period is shortened in restless legs syndrome independently from circadian rhythm. Suppl Clin Neurophysiol 56:381–389. No abstract available
Stickgold R, Walker MP (2013) Sleep-dependent memory triage: evolving generalization through selective processing. Nat Neurosci 16:139–145
Stockmeier CA, Mahajan GJ, Konick LC et al (2004) Cellular changes in the postmortem hippocampus in major depression. Biol Psychiatry 56(9):640–650
Sukys-Claudino L, Moraes W, Guilleminault C, Tufik S, Poyares D (2012) Beneficial effect of donepezil on obstructive sleep apnea: a double-blind, placebo-controlled clinical trial. Sleep Med 13:290–296. doi:10.1016/j.sleep.2011.09.014 (Epub 26 Jan 2012)
Sun H, Kennedy WP, Wilbraham D, Lewis N, Calder N, Li X et al (2013) Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. Sleep 36:259–267. doi:10.5665/sleep.2386
Suratt PM, Wilhoit SC, Brown ED et al (1986) Effect of doxapram on obstructive sleep apnea. Bull Eur Physiopathol Respir 22:127–131
Tassniyom K, Paholpak S, Tassnyom S, Kiewyoo J (2010) Quetiapine for primary insomnia: a double blind, randomized control trial. J Med Assoc Thai. 93:729–734
Taylor F, Martin P, Thompson C et al (2008) Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder; a placebo controlled study. Biol Psychiatry 63:629–632
Tergau F, Wischer S, Paulus W (1999) Motor system excitability in patients with restless legs syndrome. Neurology 23(52):1060–1063
Terzaghi M, Sartori I, Tassi L, Didato G, Rustioni V, LoRusso G et al (2009) Evidence of dissociated arousal states during NREM parasomnia from an intracerebral neurophysiological study. Sleep 323:409–412
Terzaghi M, Sartori I, Tassi L, Rustioni V, Proserpio P, Lorusso G et al (2012) Dissociated local arousal states underlying essential clinical features of non-rapid eye movement arousal parasomnia: an intracerebral stereo-electroencephalographic study. J Sleep Res 21:502–506. doi:10.1111/j.1365-2869.2012.01003.x (Epub 14 Feb 2012)
Thanacoody HK, Thomas SH (2005) Tricyclic antidepressant poisoning: cardiovascular toxicity. Toxicol Rev 24:205–214
Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, Costa J, Stiasny-Kolster K, Sampaio C (2008) Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord 23:2267–2302
Uslaner JM, Tye SJ, Eddins DM, Wang X, Fox SV, Savitz AT et al (2013) Orexin receptor antagonists differ from standard sleep drugs by promoting sleep at doses that do not disrupt cognition. Sci Transl Med 5:179ra44. doi:10.1126/scitranslmed.3005213
Van Amsterdam JG, Brunt TM, McMaster MT, Niesink RJ (2012) Possible long-term effects of γ-hydroxybutyric acid (GHB) due to neurotoxicity and overdose. Neurosci Biobehav Rev 36:1217–1227

Van der Werf YD, Altena E, van Dijk KD, Strijers RL, De Rijke W, Stam CJ et al (2010) Is disturbed intracortical excitability a stable trait of chronic insomnia? A study using transcranial magnetic stimulation before and after multimodal sleep therapy. Biol Psychiatry 68:950–955

Veasey SC, Guilleminault C, Strohl KP et al (2006) Medical Therapy for obstructive sleep apnea: a review by the medical therapy for ob- structive sleep apnea task force of the standards of practice committee of the american academy of sleep medicine. Sleep 29:1036–1044

Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P (2007) Evidence of zolpidem abuse and dependence: results of the French centre for evaluation and information on pharmacodependence (CEIP) network survey. Br J Clin Pharmacol 64:198–209

Vijayakumari AA, Khan FR, Varma RP, Radhakrishnan A (2013) Can transcranial magnetic stimulation be used to evaluate patients with narcolepsy? Neurol Sci 34:1411–1420. doi:10.1007/s10072-012-1253-0 (Epub 29 Nov 2012)

Vinkers CH, Olivier B (2012) Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective GABAA Receptor Modulators? Adv Pharmacol Sci 2012:2012:416864. doi:10.1155/2012/416864 (Epub 29 Mar 2012). http://dx.doi.org/10.1155/2012/416864. Accessed 12 Sept 2014

Wainwright SR, Galea LA (2013) The neural plasticity theory of depression: assessing the roles of adult neurogenesis and PSA-NCAM within the hippocampus. Neural Plast 2013:805497. doi:10.1155/2013/805497 (Epub 9 Apr 2013). Review. PMID: 23691371 [PubMed—indexed for MEDLINE]. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3649690/. Accessed on 10 September 2014

Walker MP (2009) The role of sleep in cognition and emotion. Ann NY Acad Sci 1156:168–197

Walker MP (2010) Sleep, memory, and emotion. Prog Brain Res 185:49–68

Walker M, Stickgold R (2004) Sleep-dependent learning and memory consolidation. Neuron 44:121–133

Walsh JK (2004) Drugs used to treat insomnia in 2002: regulatory-based rather than evidence-based medicine. Sleep 27:1441–1442

Wan H, Warburton EC, Zhu XO, Koder TJ, Park Y, Aggleton JP et al (2004) Benzodiazepine impairment of perirhinal cortical plasticity and recognition memory. Eur J Neurosci 20:2214–2224

Wang G, Grone B, Colas D, Appelbaum L, Mourrin P (2011) Synaptic plasticity in sleep: learning, homeostasis, and disease. Trends NeuroSci 34:452–463

Weaver TE, Maislin G, Dinges DF et al (2007) Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep 30:711–719

Weeks BS (2009) Formulations of dietary supplements and herbal extracts for relaxation and anxiolytic action: Relarian. Med Sci Monit 15:RA256-62

Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C (2012) Randomized clinical study of a histamine H3 receptor antagonist for the treatment of adults with attention-deficit hyperactivity disorder. CNS Drugs 26:421–434

Weng HH, Tsai YH, Chen CF, Lin YC, Yang CT, Tsai YH, Yang CY (2014) Mapping gray matter reductions in obstructive sleep apnea: an activation likelihood estimation meta-analysis. Sleep 37:167–175. doi:10.5665/sleep.3330

Whissell PD, Eng D, Lecker I, Martin L, Wang DS, Orser BA (2013) Acutely increasing δGABAA receptor activity impairs memory and inhibits synaptic plasticity in the hippocampus. Front Neural Circuits 7:146. doi:10.3389/fncir.2013.00146. eCollection 2013

Wilken JA, Kane RL, Ellis AK, Rafeiro E, Briscoe MP, Sullivan CL, Day JH (2003) A Comparison of the effect of diphenhydramine and desloratadine on vigilance and cognitive function during treatment of ragweed-induced allergic rhinitis. Ann Allergy Asthma Immunol 91:375–385

Wingen M, Bothmer J, Langer S, Ramaekers JG (2005) Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo. J Clin Psychiary 66:436–443

Winrow CJ, Renger JJ (2014) Discovery and development of orexin receptor antagonists as therapeutics for insomnia. Br J Pharmacol 171:283–293

Winrow CJ, Gotter AL, Cox CD, Doran SM, Tannenbaum PL, Breslin MJ et al (2011) Promotion of sleep by suvorexant-a novel dual orexin receptor antagonist. J Neurogenet 25:52–61 Epub 2011 Apr 8

Winrow CJ, Tanis KQ, Reiss DR, Rigby AM, Uslaner JM, Uebele VN et al (2010) Orexin receptor antagonism prevents transcriptional and behavioral plasticity resulting from stimulant exposure. Neuropharmacology 58:185–194

Wood S, Sage JR, Shuman T, Anagnostaras SG (2014) Psychostimulants and Cognition: A continuum of behavioral and cognitive activation. Pharmacol Rev. 66:193–221

Won C, Mahmoudi M, Qin L, Purvis T, Mathur A, Mohsenin V (2014) The impact of gender on timeliness of narcolepsy diagnosis. J Clin Sleep Med 10:89–95

Xu TX, Ma Q, Spealman RD, Yao WD (2010) Amphetamine modulation of long-term potentiation in the prefrontal cortex: dose dependency, monoaminergic contributions, and paradoxical rescue in hyperdominergic mutant. J Neurochem 115:1643–1654

Yaouhi K, Bertran F, Clochon P, Mézenge F, Denise P, Foret J et al (2009) A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 18:36–48. doi:10.1111/j.1365-2869.2008.00705.x

Young T, Palta M, Dempsey J et al (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328:1230–1235

Zhang J, Lam SP, Li SX, Li AM, Lai KY, Wing YK (2011) Longitudinal course and outcome of chronic insomnia in Hong Kong Chinese children: a 5-year follow-up study of a community-based cohort. Sleep 34:1395–1402

Index

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