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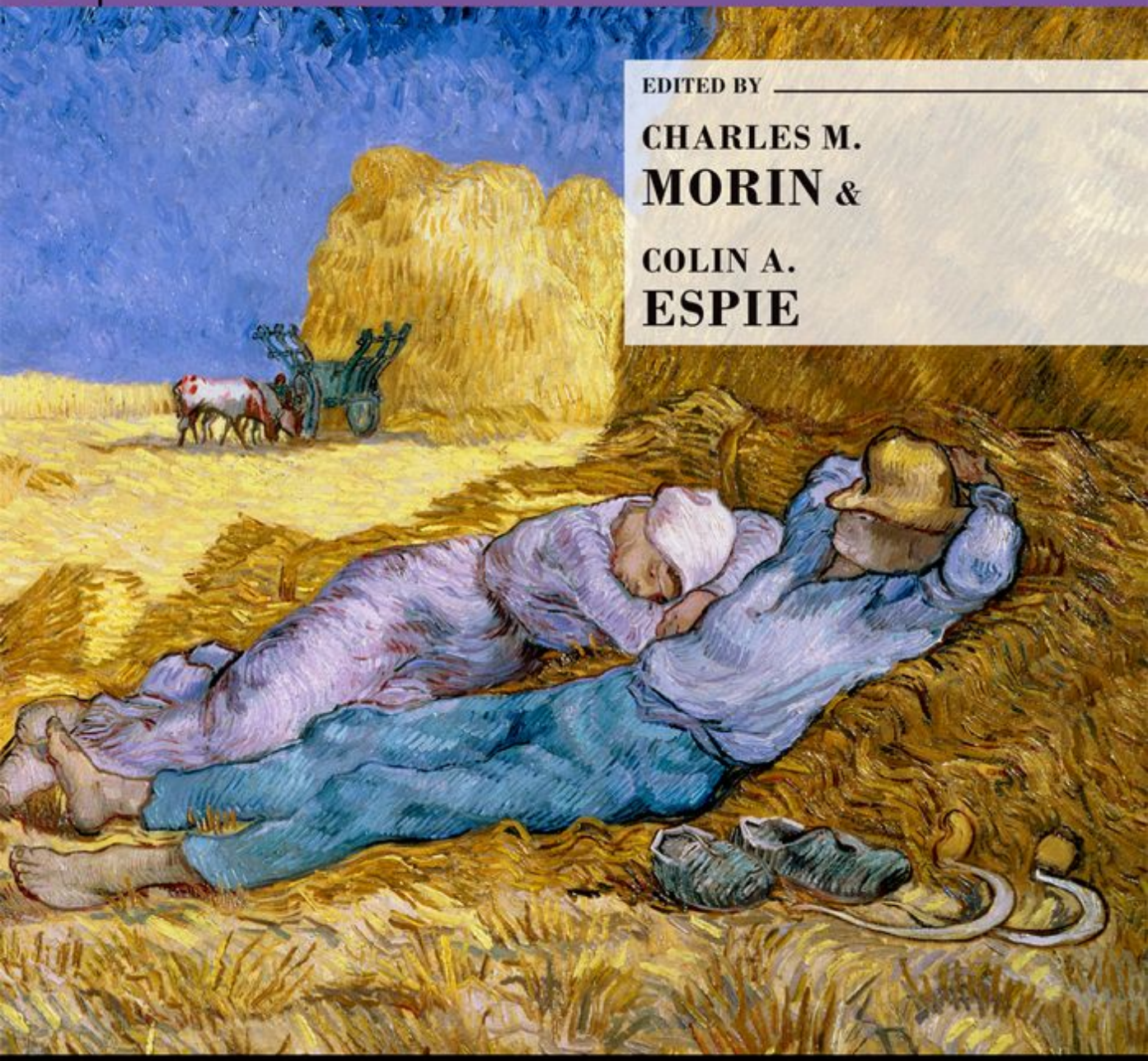

EDITED BY

CHARLES M. MORIN &

COLIN A. ESPIE

The Oxford Handbook *of* SLEEP *and* SLEEP DISORDERS

The Oxford Handbook of Sleep and Sleep Disorders

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Edited by

Charles M. Morin

Colin A. Espie

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This textbook is dedicated to our children
Geneviève and Sébastien (CMM) Craig, Carolyn and Robbie (CAE)
and to my first grand-child
Mia (CAE)

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SHORT CONTENTS

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Part Three • Sleep and Special Populations

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Introduction: Historical Landmarks and Current Status of Sleep Research and Practice

An Introduction to the Timeliness, Aims, and Scope of this Handbook

Colin A. Espie *and* Charles M. Morin

Abstract

The purpose of this brief, introductory chapter is to "set the scene" for the handbook. We start by providing some historical context on the understanding of sleep across the ages, from ancient times through to more contemporary landmarks. From this we learn that sleep has always been a fascinating subject. It captivated the thinking of early philosophers and emerged as a subject of scientific interest in medieval times. However, many of the discoveries that have begun to unlock the mysteries of sleep have taken place within living memory. We also foreshadow the current status of sleep research and practice that forms the substance of the handbook. These are exciting times, not least for psychologists and cognitive behavioral scientists. A great deal of progress has been made in the characterization, assessment, and treatment of sleep disorders in recent years, and the new discipline of behavioral sleep medicine has grown out of this scientist–practitioner emphasis. The chapter concludes with an outline of the aims and scope of the handbook and an overview of its main sections. We also introduce each chapter and its author(s). We hope that you will find the handbook stimulating and helpful in your clinical and research practice.

Keywords: sleep, sleep disorders, behavioral sleep medicine, research, treatment, history

History and landmarks

We all sleep, and we all must sleep. Indeed, sleep is by no means an exclusive feature of human physiology and behavior. All other mammals sleep too, albeit in some cases with adaptations. For example, prey species may have to delay sleep for periods of time to avoid being eaten, and the blind Indus dolphin sleeps in very short bursts to ensure safe navigation. Insects like the fruit fly also display sleep-like states in their rest–wake cycles. Indeed, it is fair to say that sleep, in some form, appears to provide restoration for all living organisms. Even plants have a time-keeping, circadian clock mechanism, allowing them to "anticipate" daily changes in light and temperature. Despite such seemingly universal imperatives, the study of sleep processes and functions is still in its infancy. The same applies to our understanding of disorders of sleep. Nevertheless, it is a fascinating scientific and clinical area, and progress is certainly being made.

An early history of sleep

Of course we know relatively little about sleep in primitive times, but we can deduce enough to be certain that sleep is no modern invention! For example, it has been suggested that Neanderthal man (70,000 to 40,000 BC) may have represented a transitional stage between the non-human primate pattern, which was of polyphasic sleep (multiple rest–activity cycles in a 24-hour period) and the monophasic pattern (sleep at night, awake by day) that we are familiar with in modern times. Monophasic sleep is thought to have become dominant in the Neolithic period (10,000 BC). By the time we come to the early civilizations of Mesopotamia, India, Egypt, and China, people appear to have been aware of the importance of sleep and dreams, with documented remedies ranging from divination and chanting to blood-letting, and the use of medicinal plants to promote sleep or wakefulness. Indeed, the yin-yang symbol attributed to the

ancient Chinese (ca. 2900 BC) was adopted by the American Sleep Disorders Association (now the American Academy of Sleep Medicine) as its emblem.

Likewise, there are many references to sleep in ancient literature. The Bible, for example, refers to sleep being associated with contentment and hard work but also with laziness, and dreaming is seen as a means of communication between God and man in many religions. The Greek philosopher Hippocrates (ca. 460 BC) suggested that sleep resulted from blood moving from the limbs to be warmed in the "inner regions" of the body. Aristotle in the 4th century BC believed that dreams were portents of the future, but also suggested that the ingestion of food indirectly induced sleepiness by taking heat away from the brain. Sleep was also used as a synonym for death in ancient Rome and Greece by poets such as Homer and Ovid.

Moving on to more recent times, by the end of the first millennium a scientific influence had become more dominant, reducing the previous emphasis on philosophy and mysticism. The uses of medicinal plants continued, but behavioral recommendations also began to emerge. For example, the Jewish philosopher Maimonides in the 12th century stated that "the day and night consist of 24 hours. It is sufficient for a person to sleep one third thereof, which is 8 hours. These should be at the end of the night so that from the beginning of sleep until the rising of the sun will be 8 hours. Thus he will arise from bed before the sun rises." A theory on sleep mechanisms was proposed by René Descartes in the 17th century. His hydraulic model of sleep suggested that the pineal gland helped to maintain alertness and that the "loss of animal spirit" from the pineal gland caused the ventricles to collapse, thereby inducing sleep. Thomas Willis and Thomas Sydenham a little later first developed what might be seen as the emergent clinical neurology of sleep, with work including the first references to restless legs syndrome, and also contributions on nightmares and insomnia.

Some modern landmarks in our understanding of sleep

Some of these latter insights are suggested by Dement (1998) to have occurred too early to be exploited by the as-yet-unborn field of sleep medicine. In this context he also mentions other scientific landmarks such as the demonstration of the persistence of circadian rhythms in the absence of environmental cues by De Mairan (1729), and Gellineau's publication of a description of the narcolepsy syndrome in 1880. Likewise, Caton demonstrated electrical rhythm in the brains of animals in 1875, and Hans Berger's early descriptions of the differences between brain wave patterns in awake and sleeping brains continued the perspective that sleep was essentially the brain turned off, the so-called "passive process theory."

Since the early 1950s, discoveries about sleep seem to have increased almost exponentially, revealing that sleep is a varied, complex, and active arrangement of processes. Starting with the "discovery" of rapid eye movement (REM) sleep in 1952 by Aserinsky and Kleitman, the relationship between eye movements and dream activity was reported by Dement, who later also demonstrated the effects of sleep deprivation upon REM sleep in 1960. At around the same time, Jouvet showed that, during REM sleep, the voluntary muscle groups are essentially paralyzed, and by the mid 1960s the essential features of sleep had become established to the extent that a standardized manual for the scoring of human sleep had been published by Rechtschaffen and Kales. In parallel to the growing recognition of the importance of "homeostatic regulation"—sleep deprivation leads to growing sleep debt and increased pressure to sleep—seminal work was being carried out looking at circadian influences relating to sleep and wake timing: the so-called "body clock." As early as 1938, Kleitman and his graduate student had conducted heroic personal experiments on circadian function by sleeping for a month in the depths of Mammoth Cave (Kentucky). They were trying to find out if our 24-hour rhythm is simply a reaction to environmental circumstances. However, it was not until the 1960s that Aschoff described the complexity of the cyclic sleep–wake pattern. Borbély (1982) would later publish his "two-process model" of sleep regulation, demonstrating the interaction between homeostatic and circadian functions. The discipline of chronobiology was now well and truly born.

Extending from the work of Konopka and Benzer on fruit flies in the early 1970s, other researchers over the past 30 years (e.g., Rosbash, Young, Takahashi) have provided clear evidence of specific "clock genes." Despite the fact that we live in a 24-hour world, it is of considerable interest that the human biological clock appears to be set slightly longer than 24 hours. The discovery that people who are cortically blind would naturally follow what is called a "free-running schedule" with progressive phase delay in their sleep onset has been associated

with recognition that our circadian system is influenced by the availability of light to "entrain" the sleep–wake cycle to a 24-hour period, with the endogenous hormone melatonin playing a crucial role in the timing of sleep and wakefulness. The interaction of the sleep homeostat with circadian timing mechanisms is now recognized as a mutual feedback process (Czeisler, Dijk), and highly productive laboratory studies have gone on to demonstrate a relationship between circadian physiology, sleepiness, and human performance.

Interest in the phenomenon of sleepiness has evolved from distinctive scientific and clinical areas of enquiry. From those who were interested in the essential nature of sleepiness, its causes, and its consequences (such as Dinges), to those who became particularly interested in the risks associated with undertaking waking tasks while sleepy (not least driving; Phillips; Akerstedt; Mitler) and those who were interested in sleep disorders where excessive daytime sleepiness was a hallmark feature. Sleep apnea was reported independently by two research groups in France and Germany in 1965, following Lugaresi's recognition of the relationship between hypersomnia and periodic breathing. The most important development in the treatment of obstructive sleep apnea (OSA), however, came from Australia in the 1980s, where Sullivan developed a novel but simple preventive treatment that has become known as CPAP (continuous positive airway pressure).

Excessive daytime sleepiness is also the cardinal feature of the primary hypersomnia problem that has become widely known as narcolepsy. As previously mentioned, clinical descriptions of narcolepsy have been available for a very long time, but it was not until the early 1970s that canine narcolepsy provided a unique animal model in which to study the disorder. The discovery of a hypocretin/orexin mutation in narcoleptic Doberman pinchers (Mitler) later led to the observation that narcolepsy is associated with HLA-DR2 and the hypothesis that narcolepsy may result from an autoimmune insult to the central nervous system. It is now known that complex HLA-DR and DQ interactions confer risk of the narcolepsy with cataplexy syndrome (Mignot).

Excellent and very readable overviews of such early influential times have been published by William Dement (*The Promise of Sleep*) and by Peretz Lavie (*The Enchanted World of Sleep*), and these books are recommended to the reader. Changing social and cultural factors are also very important—just consider for example the influence of the invention of the light bulb and the subsequent widespread availability of electric light. Those interested in sleep through the ages will also find fascinating insights in Michael Thorpy's *A History of Sleep in Man*.

Insomnia and the past 50 years

Before closing this section on landmarks, it is important not to neglect the most common sleep disturbance of all: insomnia.

Modern approaches to the management of insomnia have been dominated by pharmacological agents, certainly until the early 1970s. In the 19th century, bromides and chloral hydrate were primarily used, later supplanted by barbiturates in the first half of the 20th century. Though effective as sleep aids, barbiturates proved to be dangerously addictive and very unsafe in overdose. Consequently, scientists developed a new group of drugs known as benzodiazepines, which, although safer in profile, nonetheless proved problematic in withdrawal. Some also had troublesome carryover effects, and so "z" drug variants called benzodiazepine receptor agonists became more popular from the 1990s onward. The potential role of pharmaceutical-grade melatonin has also attracted increasing interest in the past 15 years with the development and testing of melatonin receptor agonists. More recently still, there has been interest in orexin antagonist drugs for insomnia. Worryingly, however, in real-world practice much of the prescribing for insomnia is now off-label, that is, with drugs designed for another purpose but that have sedative side effects, such as sedative antidepressant medications (Feren, Schweitzer, & Walsh, 2011).

From a behavioral perspective, pioneering work in the 1970s by Bootzin, who recognized that sleep falls under the control of operant principles, and by Hauri and de la Peña, who recognized the psychophysiological nature of insomnia and the so-called "reverse first night effect," respectively, spawned interest in insomnia amongst psychologists. Such models led to greater interest in insomnia as a disorder of hyperarousal (e.g., Bonnet, Nofzinger) and in the crucial role of cognitive factors (e.g., Borkovec) in its genesis and maintenance. Not surprisingly, variants of relaxation were among the first forms of psychological treatment along with paradoxical logotherapeutic methods (Ascher) and further developments of Bootzin's stimulus control model. The 1980s saw the emergence of the extended stress-diathesis model of

insomnia and a novel intervention based on time-in-bed restriction (Spielman & Glovinsky). It was around this time that we (Espie, Morin) and others (e.g., Lack, Edinger) came into the field, conducting clinical trials of insomnia interventions across a range of populations. Gradually, a more integrated cognitive behavioral framework of insomnia has emerged. The first head-to-head studies of CBT versus pharmacotherapy were published in the 1990s and later repeated when the newer benzodiazepine receptor agonist medications became more popular in the early 2000s. Both types of treatment showed short-term benefits, but psychological and behavioral approaches have consistently demonstrated superiority in longer-term outcomes (Riemann & Perlis, 2009), being endorsed as such since the 1990s in national guideline documents (e.g., NIH in the U.S., and NICE and BAP in the UK).

Over the past 20 years, research on insomnia has progressed in several ways. There have been important advances in measurement using patient-reported outcomes. This began substantially with the publication of the Pittsburgh Sleep Quality Index (Buysse), and later with the Insomnia Severity Index (Morin). Likewise there has been progress in understanding cortical correlates of insomnia through studies using quantitative EEG analysis (e.g., Perlis, Jacobs) and brain imaging (e.g., Nofzinger, Riemann, van Someren). We also better understand the epidemiology of insomnia (Ohayon, Lichstein) and its societal impact, and have robust research diagnostic criteria (Edinger) to apply across a range of study methodologies. There has also been a return to the experimental laboratory, investigating arousal/de-arousal mechanisms that could be important in the genesis and maintenance of insomnia. Studies range from the role of perception, worry, and cognition (Harvey), attentional inhibitory mechanisms (Espie), and cortical arousal conditioning (Perlis) to animal models of insomnia (Saper, Cano). There continues to be a primary focus upon CBT interventions, but there is growing interest also in other forms of psychotherapy, particularly the so-called "third wave" therapies including Mindfulness and Acceptance and Commitment Therapy (e.g., Lundh, Ong, Gross). There is also some novel work using in-lab reconditioning treatments such as Intensive Sleep Retraining (Lacks).

Current status of sleep research and clinical practice

It is clear that much progress has been made in understanding sleep and its disorders. Thinking particularly on the "behavioral" side of sleep research, candidate models and mechanisms associated with the development and persistence of insomnia have been proposed, and effective treatments have been developed and tested. However, behavioral sleep medicine has emerged as an area of special emphasis, conveying a broader interest, beyond insomnia, to other disorders of sleep and wakefulness, and beyond CBT to other possibilities for intervention.

Beyond an interest in insomnia

Some examples include important work on REM and NREM parasomnias, where psychophysiological models and treatments seem as relevant as they do in insomnia (Germain, Krakow). Nightmares associated with PTSD and the exacerbation of sleepwalking or night terrors at times of stressful change seem appropriate territory for psychological formulation and treatment. Other examples include circadian aspects of normal and dysregulated sleep where behavior, lifestyle, mental health, or disability factors may reciprocally influence circadian physiology through social timing and patterning as well as through exposure to light cues. Such biopsychosocial models can also inform care provision for vulnerable groups.

We know from many fields of health care that behavior change is challenging. Prescribing the "solution" is often relatively easy. Having a plan to eat well, lose weight, exercise more, stop smoking, and drink only in moderation is both a personal and national pastime. But turning knowledge and intention into healthy behavior is difficult and is mostly neglected in traditional medical practice. Consider nCPAP as a treatment for OSA. The treatment is a simple mechanical one to maintain physiological function: keep the airway open and you will breathe normally during sleep—but treatment implementation is essentially behavioral. Research on predictors of outcome tells us that using the mask leads to improvement, whereas not using it does not lead to improvement. Health psychology and behavior change models are beginning to be influential here (e.g., Aloia, Bartlett).

We will have more to say in the final chapter on the research agenda looking ahead. However, it is already clear that seeing sleep disorders as psychophysiological propositions may be an important theme. Within the psychological component we need to consider perception, attention, memory, learning, reasoning, contemplation, action, adherence, and relapse on the cognitive behavioral plane; we also need to consider meaning, values, relationships,

mood, and sense of control on the emotional plane. These are just examples, not an exhaustive list. Likewise, when it comes to the disorders themselves, we have to recognize the importance of phenotypes (and homogeneity) while accounting for individual differences (heterogeneity), so that ultimately we may answer complex questions such as *"How much of what will effect which changes in whom?"* and *"Why, how, and when will these effects happen?"* Moreover, to continue to move the field forward, it will be important to have larger studies on better defined populations using common methodologies that integrate psychology and neuroscience approaches (e.g., van Someren, Riemann) and to make better use of experimental paradigms such as those that have guided the discovery that memory functions are sleep-stage dependent (e.g., Walker, Drummond).

Professional societies and learned journals

Associated with such progress in sleep research, and bridging across to progress in sleep medicine, there are now six firmly established specialized journals that have the word "sleep" in their title. The official journal of the European Sleep Research Society, the *Journal of Sleep Research* was first issued in 1992 (http://www.wiley.com/bw/journal.asp?ref=0962-1105&site=1), and *Sleep and Biological Rhythms* (published by the Asian Sleep Research Society) was first published in 2003 (http://www.blackwellpublishing.com/journal.asp?ref=1446-9235&site=1). With an even longer history, *SLEEP*, the house journal of the American Academy of Sleep Medicine, has been in continuous publication since 1978 (http://www.journalsleep.org/). Moreover, in 2005, the *Journal of Clinical Sleep Medicine* was added to the AASM stable (http://www.aasmnet.org/jcsm/). *Sleep Medicine Reviews* (http://www.elsevier.com/wps/find/journaldescription.cws_home/623074/description#description) and *Sleep Medicine* (http://www.elsevier.com/wps/find/journaldescription.cws_home/620282/description#description) became available in 1997 and 2000, respectively, and the specialized journal *Behavioral Sleep Medicine* was first published in 2003 (http://www.informaworld.com/smpp/title~content=t775648093~db=all). The gross effect of this expansion in journal publication is that in 2010 alone there were around 600 papers published on sleep across these six journals alone, with many more of course appearing elsewhere. It should be noted, in addition, that some of the national sleep societies produce other publications that contain valuable science and professional information. A notable example of this is the Sleep Research Society's *SRS Bulletin*, which was in its 17th year of publication in 2011.

Another fundamental link between research and practice is education. In the U.S., the American Academy of Sleep Medicine (www.aasmnet.org/) and the Sleep Research Society (http://www.sleepresearchsociety.org/) work together on many educational activities, not the least of which is the Association of Professional Sleep Societies' meeting (now simply called "SLEEP"), held in the early summer every year. This meeting now attracts around 6,000 delegates. Some other continental and national societies, like the European Sleep Research Society (www.esrs.eu/cms/) and the Canadian Sleep Society (www.css.to/), continue to have both basic sleep research and clinical research and practice integrated within the same society. The World Federation of Sleep Research and Sleep Medicine Societies (www.wfsrsms.org/), now abbreviated to the World Sleep Federation, provides an overarching organizational structure for the sleep research societies worldwide and holds quadrennial scientific meetings. The WFS Governing Council is the ruling group made up of delegates from member societies (ESRS, ASA, ASRS, SRS, AASM, CSS, and FLASS), thus representing over 10,000 researchers and clinicians involved in the sleep field worldwide. The World Sleep Federation was founded in 1987. More recently, the World Association of Sleep Medicine (www.wasmonline.org/) was founded to provide further impetus to clinical aspects of sleep and the advancement of sleep health worldwide.

Over the past 50 years, there has also been a worldwide growth of sleep medicine centers, dedicated to the assessment and treatment of sleep disorders. The most enlightened sleep centers are truly interdisciplinary in nature, comprising physicians, clinical psychologists, nurses, technologists, and a wide range of other professionals including dentists, physiologists, and educationalists. The medical profession has been the first to incorporate sleep into the curriculum for formal training; for example, the American Medical Association now recognizes sleep medicine as a sub-specialty area. Likewise, the American Academy of Sleep Medicine, having for a while acknowledged behavioral sleep medicine as an emerging area, has recently incorporated the Society for Behavioral Sleep Medicine (http://www.behavioralsleep.org/) in the following terms: "*Behavioral Sleep Medicine is the field of clinical practice and scientific inquiry that encompasses: the study of behavioral, psychological, and physiological factors underlying normal and disordered sleep across the life span;*

and, the development and application of evidence-based behavioral and psychological approaches to the prevention and treatment of sleep disorders and co-existing conditions." A similar approach is developing in other countries as well. The European Sleep Research Society, for example, is involved in the development of a core curriculum for specialists from diverse professional backgrounds and will ultimately license physicians, psychologists, nurses, scientists, and sleep technologists. National societies within the framework of WSF are also involved in the accreditation of sleep centers as clinical and research environments.

Another feature of the work of national societies has been the commissioning and reporting of guideline groups to review scientific evidence in different fields of sleep medicine practice. Papers arising from this work, like the AASM Practice Parameter statements, are regularly published in scientific journals and provide a ready source of high-quality information to guide the practitioner in selecting assessment and treatment techniques. Likewise, systematic reviews and meta-analyses provide scientific rigor to the summarizing of treatment outcome studies. Moreover, independent groups from government or government agencies have provided external scrutiny of the field, such as the National Institutes of Health (U.S.) and the National Institute for Health and Clinical Excellence (UK). The systematization of the sleep disorders, and greater consistency in approaches to assessment and management, has been aided by the development of a specific International Classification of Sleep Disorders system, currently in its second version (ICSD-2). Somewhat in parallel, the American Psychiatric Association work groups have produced several insomnia classifications over the years, with DSM-5 due for publication soon.

In all these ways, sleep seems to be an area of fast-developing interest. Needless to say, improvements in assessment and treatment services are hugely popular amongst patients who have often felt that their sleep problems and their impact on day-to-day life have been largely neglected by health-care systems. Slowly but surely this is changing. The growth of sleep centers in the U.S. first began in the 1960s; however, it has to be said that sleep services remain patchy across disorders and patchy around the world. For example, services for people with persistent insomnia or insomnia associated with psychiatric or medical disorders are generally poorer than those for sleep apnea and narcolepsy. Nevertheless, the scale of the insomnia challenge at community and primary care levels has been identified, and consideration has been given to the use of a "stepped-care" model to meet these needs (Espie). There is growing awareness too of restless legs syndrome and of periodic limb movement disorder, whereas the parasomnias, particularly non-REM parasomnias (such as sleepwalking and night terrors), are probably under-diagnosed and under-treated. It is striking that in this latter area, for example, there is very little evidence of what treatments actually work.

Aims and scope of this handbook

Having considered some of the historical landmarks in the field of sleep research and practice, and having also outlined some aspects of its current status, we hope that we have persuaded you of the timeliness of producing this handbook. Our vision has been to compile a resource that will meet the needs of psychologists in particular, but also other professionals who have an interest in sleep and sleep disorders. To achieve this, we are thrilled that each chapter in the handbook is authored by eminent international figures. If the handbook works as a source of educational, clinical, and indeed inspirational material, it is largely to their credit.

The handbook is divided into three main sections: Section I: Sleep; Section II: Sleep Disorders; and Section III: Sleep and Special Populations.

In Section I on Sleep, there is a total of 14 chapters exploring the nature and functions of sleep, from individual through societal perspectives. Philippe Peigneux's chapter *sleep and the brain* is followed by chapters on *the regulation of human sleep and wakefulness* (Derk-Jan Dijk) and on *the functions of sleep* (Yvonne Harrison). Having provided this platform for an understanding of sleep itself in Chapters 1–3, this first section then pursues the relationships between *sleep and human development* (Kathryn Lee); *sleep and human performance* (Tim Monk); *sleep, cognition, and cognitive neuroscience* (Matt Walker); *sleep and emotion* (Martica Hall); and *sleep and dreaming* (Joseph de Koninck) in Chapters 4–8. Particular consideration is then given in Allison Harvey's Chapter 9 to *sleep and psychopathology*, followed by Chapter 10 on *sleep and psychotropic drugs* by Dieter Riemann. Section I concludes with Chapters 11–14 devoted to *societal aspects of sleep* (Sara Arber), *sleep and public health/safety* (Torbjorn Akerstedt), and consideration of *gender factors in sleep* (Helen Driver). The closing chapter by Jason Ellis considers the relationship between *sleep and the psychology curriculum for university education*.

Section II on Sleep Disorders comprises a further 18 chapters divided into two subsections. Chapters 15–19 consider the epidemiology, classification, and assessment of sleep disorders. *Epidemiology* is covered by Kevin Morgan, with further chapters providing a *socioeconomic perspective on sleep* (Damien Leger), consideration of *forensic aspects of sleep disorders* (Rosalind Cartwright), *classification and diagnosis* (Jack Edinger), and *clinical assessment techniques* (James Wyatt). There then follows 13 chapters on the sleep–wake disorders. The first three of these are on *insomnia, etiology, and conceptualization* (Michael Perlis); *behavioral and physiological assessment* (Celine Bastien); and *insomnia therapeutic approaches* (Ken Lichstein). Chapters 23 and 24 are on *sleep and psychiatric disorders* (Rachel Manber) and *sleep and medical disorders* (Leanne Fleming and Judith Davidson), respectively. *Sleep and substance abuse* is covered by Todd Arnedt, and two chapters are devoted to parasomnias: the first is on *nightmares* (Anne Germain) and the second on *night terrors and somnambulism* (Anthony Zadra). In Chapters 28–30, circadian rhythm disorders are described by Leon Lack (*phase-advanced and phase-delayed syndromes*) by Annie Vallieres (*shift work*), and by Tracey Sletten and Jo Arendt (*jet lag*). In Chapter 31, Terri Weaver explores s*leep-related breathing disorders*, followed by Yves Dauvillier's overview of *hypersomnia and narcolepsy* and Richard Allen's chapter on *restless legs syndrome and periodic limb movement disorder.*

The handbook concludes with Section III on Sleep and Special Populations. Over the course of Chapters 34–39, expert information is provided on *sleep-related problems in childhood* (Jodi Mindell), in *adolescence* (Amy Wolfson), in *older adults* (Sonia Ancoli-Israel), in people with *learning disability* (Luci Wiggs), in people with *brain injury* (Marie-Christine Ouellet), and in people experiencing *chronic pain* (Michael Smith).

Conclusion

Thirty or forty years ago the importance of diet and exercise to health and well-being was barely acknowledged in mainstream science or clinical practice. At some level everyone knew of their importance, but they were lifestyle factors, lifestyle choices, were they not? How much has changed since then! Now they are major health policy drivers and cost headings. Their influence on health and health outcomes is highlighted on every medical and health professional course, they are routinely measured by various indices, and they are actively promoted and their adverse consequences treated in every community and on every hospital campus.

So the story goes for sleep, and sleep's time has come!

From the ancient to the present day, the importance of sleep has seldom been disputed, but it has never had top billing. It seems that the combined critical mass of research, the needs of the population, and the shifting weight of professional interest is now pushing sleep onto center stage.

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PART 1

Sleep

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CHAPTER

1 Sleep and the Brain

Philippe Peigneux, Charline Urbain, *and* Remy Schmitz[1]

Abstract

The phenomenological experience of sleep as a cessation of waking activity is misleading. Indeed, it suggests that sleep constitutes, like a switch, a simple mechanism by which are shut off all neurophysiological processes associated with an active and costly wake state of vigilance. In this chapter, we present a summary description of sleep and its defining features, viewed from behavioral, neurobiological, neurophysiological, and functional neuroanatomical perspectives. Given the universality of sleep and/or sleep-like phenomena across animal species, we review also the phylogenesis of sleep. As the reader will realize, the simplistic view that sleep is a mere state of inactivity must be replaced by the conception of a complex, multidimensional, and active state of the brain.

Keywords: NREM, REM, SWS, USWS, neurobiology, neurophysiology, functional neuroanatomy, phylogenesis, EEG, PET, fMRI, MEG

At the behavioral level, sleep presents a number of definite features that humans share with most animal species (Borbély, Hayaishi, Sejnowski, & Altman, 2000). It is a state of physical quiescence, characterized mostly by no or minimal movements, closure of the eyes, and a stereotypic body posture (e.g., in humans, lying down or curling; in bats, hanging upside down). As compared to quiet wakefulness, there is also reduced responsiveness to external stimulation during sleep. Additionally, rapid reversibility between states (e.g., the fact that the sleeper will wake up if the stimulation is reasonably distinctive and/or the need for sleep is exhausted) distinguishes sleep from other specific states of altered vigilance like coma, brain death, hypothermia, or hibernation.

However, behavioral observations alone are usually not sufficient to ensure that the individual under scrutiny is genuinely sleeping, rather than being in a relaxed state of wakefulness or in an intermediate state of drowsiness. Furthermore, mere observation cannot capture the dramatic changes in cerebral activity from wakefulness to sleep, nor the fact that sleep is composed of two distinct physiological stages: non-rapid eye movement (NREM) and paradoxical or rapid eye movement (REM) sleep. In humans, NREM sleep is further subdivided into three stages according to sleep depth (Silber et al., 2007), from the intermediate stage 1 sleep (drowsiness and sleep onset) to light stage 2 sleep to the deepest stage 3 sleep, also known as slow-wave sleep (SWS). Under normal nocturnal conditions, NREM always precedes REM sleep within an ultradian cycle lasting on average 90 minutes and repeating itself (Figure 1.1), with the consequence that the sleeper may complete up to five cycles in a typical night (Dement, 1978).

Additionally, sleep is a regulated phenomenon whose timing and duration are contingent upon two main processes: homeostatic and circadian (Borbély, 1982; Daan, Beersma, & Borbély, 1984; see Figure 1.2). During the course of a normal day–night cycle, the pressure for sleep continuously

[1]CU and PP equally share first authorship

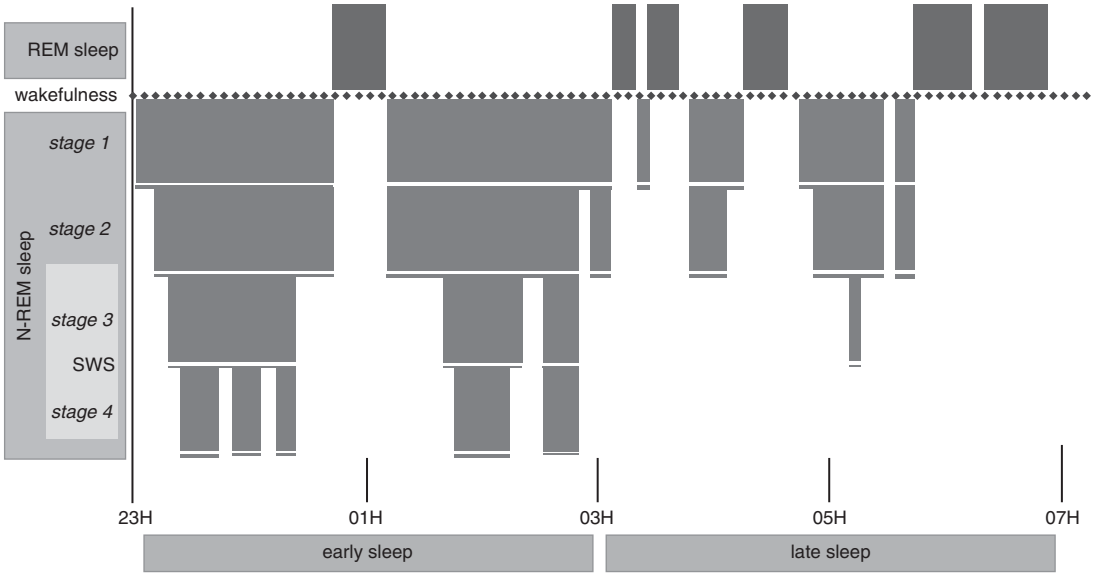


Fig. 1.1 Hypnogram illustrating sleep stages and their cycle in the course of a canonical night in a healthy young sleeper. Gray bars indicate changes in sleep stages (or wakefulness) across time. Note the progressive decrease in NREM sleep prevalence from the first half to the second half of the night, whereas the reverse pattern is observed for REM sleep.

accumulates with time spent awake, then dissipates during the night of sleep. Extending the waking period above normal levels (e.g., in a sleep deprivation protocol) results in a sleep debt with a rebound on the subsequent night where both duration and intensity are increased, demonstrating the homeostatic regulation of sleep. This gradual change in sleep pressure is counterbalanced by the circadian process, e.g., a nearly 24-hour endogenous oscillatory variation in alertness and sleep propensity. The circadian signal for sleep/alertness is high/low in the early hours and low/high in the evening, with the consequence that homeostatic and circadian processes work in opposition during the day but in synchrony during the night to ideally ensure consolidated periods of wakefulness and sleep. The interaction between these two processes also exerts an influence on variations in cognitive performance throughout the day, especially in the attentional domain (Schmidt, Collette, Cajochen, & Peigneux, 2007; Schmidt et al., 2009). Due to the close relationship between slow-wave activity (SWA) in SWS and sleep pressure dissipation (e.g., the homeostatic process) along the night of sleep, the first half of the night is particularly rich in slow-wave activity (about 80% of time), whereas in each subsequent cycle the length of REM periods increases while the length of deep SWS decreases (Figure 1.1) and the amount of stage 2 sleep remains fairly constant.

It was Hans Berger who in 1929 performed the first recording of the electrical activity of the brain, which he named electroencephalography (EEG). He described different oscillation patterns in the EEG, the best known being the Berger's wave or alpha (8–12 Hz) occipital rhythm, observable during quiet wakefulness but suppressed by the opening of the eyes. He also showed first that the frequency of EEG oscillations slows down with sleep, followed by Loomis, Harvey, & Hobart (1937), who divided sleep into five levels (A to E) representing the spectrum of waking to NREM sleep stages 1–4. REM sleep was only later discovered as a distinct stage of sleep, with low-voltage rapid oscillations in brain activity, muscular atonia, and rapid ocular movements (Aserinsky & Kleitman, 1953). These findings and the availability of electrophysiological and physiological techniques (see Information Box 1.1) eventually led to the first consensus on how human sleep should be recorded and scored: the "Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects," published by Rechtschaffen and Kales (1968). Although technological advances have allowed the development of novel methods for the analysis of sleep (e.g., spectral analysis is thought to better reflect specific discharge

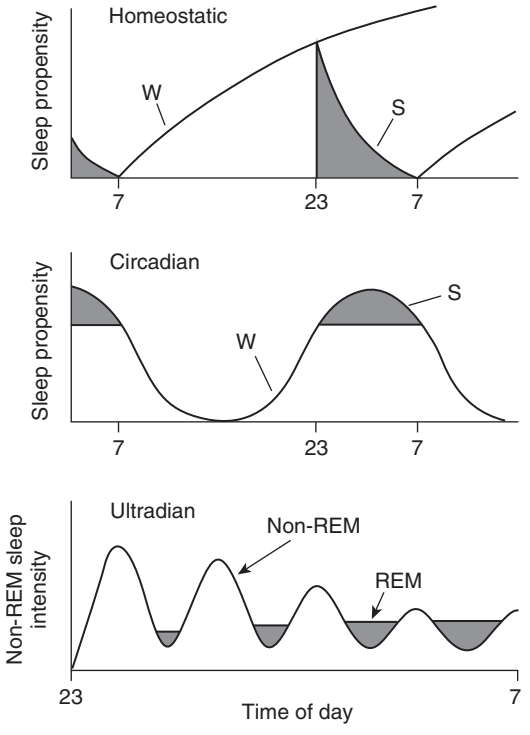


Fig. 1.2 Schematic representation of the three main processes involved in the regulation of sleep. The homeostatic process maintains sleep propensity (duration and intensity of sleep), which builds up during wakefulness and declines during sleep. The circadian process is a nearly 24-hr endogenous oscillatory variation that determines the timing of the propensity to sleep. Ultradian mechanisms underlie the NREM–REM sleep cycle. As the sleep episode progresses, the intensity of NREM sleep declines and the duration of successive REM sleep intervals increases. W: awake state; S: sleep. From Borbély et al. (2000).

patterns observed at the cellular level in NREM sleep stages; Corsi-Cabrera, Guevara, Del Rio-Portilla, Arce, & Villanueva-Hernandez, 2000; Corsi-Cabrera, Munoz-Torres, Del Rio-Portilla, & Guevara, 2005), the classification and codification of sleep patterns still remains performed more than 40 years later upon visual and computer-based inspection of 30-second polysomnographic epochs of electroencephalographic (EEG), electrooculographic (EOG), and electromyographic (EMG) signals, following international consensus guidelines recently revised in the "New Sleep Scoring Manual" (Iber, Ancoli-Israel, Chesson, & Quan, 2007), which we will use below to delineate the different stages of sleep and wakefulness (see also Summary Table 1.1 at the end of this section).

Wakefulness

Wakefulness can be defined as a state of full consciousness, allowing interaction with the environment. In humans the waking EEG is characterized mostly by a so-called desynchronized pattern of neuronal firing, reflected in the EEG by rapid, high-frequency waves in the beta (β) range (14–40 Hz) with low amplitude (10 to 30 μV) and high muscular tonus at the EMG. When subjects are awake in a quiet, relaxed state or resting, especially with eyes closed, EEG recorded from the posterior part of the brain (mostly at occipital locations) displays patterns of alpha (α) or Berger waves of lower frequency (8–12 Hz) and increased amplitude (20 to 40 μV; Figure 1.3), reflecting the increased synchrony of underlying neural activity in non-stimulated brain regions (Borbély et al., 2000).

NREM sleep

NREM sleep stages are characterized in humans by regular respiration, decreased muscular tonus, and gradual slowing down of the EEG frequency patterns with increasing amplitude (Figure 1.3), from stages N1 to N2, or light sleep, to N3, or deep slow-wave sleep (SWS), reflecting the progressive synchronization of activity within and between neuronal populations. Spectral analyses additionally reveal a background pattern of slow-wave activity (SWA) below 1 Hz (Achermann & Borbély, 1997), not visually apparent in the EEG recording but having important physiological implications (Steriade, Contreras, Curro Dossi, & Nunez, 1993). Superimposed on slow rhythmic activities are transient events, mainly K-complexes and sleep spindles in N2 whose recurrence (every 3–10 seconds) is regulated by the underlying SWA (Steriade & Amzica, 1998).

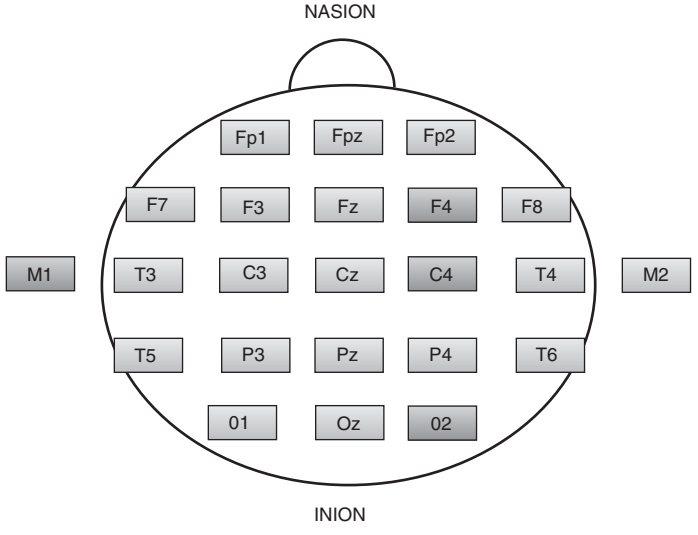
NREM sleep stage N1 and sleep onset

NREM sleep stage N1 is a drowsiness transition period between wakefulness and sleep. Stage N1 is characterized by the occurrence of theta (θ) waves in the EEG, slower in frequency (4–8 Hz) and greater in amplitude (50 to 100 μV) than alpha (α) waves; a decrease in muscular activity; and slow eye movements. A valid electrophysiological marker of sleep onset is the attenuation of the alpha rhythm, which signs the transition from relaxed wakefulness to stage N1. It is therefore important to record EEG at occipital derivations where the alpha rhythm is prominent to accurately determine sleep onset (Silber et al., 2007). At the behavioral level, subjects start failing to respond at the presentation of auditory tones, although awakening thresholds remain low, to the point that subjects awoken during this stage may often report not having been asleep at all.

Box 1.1 Polysomnographic Techniques

Polysomnography is the multi-modality recording of sleep using an array of electrophysiological and physiological techniques allowing the analysis and scoring of sleep. The main measures are electroencephalography, electrooculography, and electromyography.

1. **Electroencephalography (EEG)** records electrical activity produced by synchronous postsynaptic potentials of brain neurons. Recording is made possible using metal current conductor electrodes placed in contact with the scalp. The resulting signal is amplified and digitized, filtered, and cleaned from artifacts, then examined for rhythmic and transient activities. Rhythmic activities are continuous oscillations patterns in the EEG that vary in frequency (cycles per second, expressed in Hertz [Hz]) and amplitude (expressed in microvolts [μV]). Transient activities are isolated, short-duration events with characteristic features (e.g., K-complexes, vertex waves, and spindles in sleep; see main text). When the EEG is recorded at multiple scalp locations according to international conventions (e.g., the 10-20 systems; see Information Box Figure 1.1 below), it additionally allows topographic, spatially based analysis of specific sleep patterns (Finelli, Borbély, & Achermann, 2001).



Information Box Fig. 1.1 International 10-20 system for topographical disposition of the electrodes on the scalp (simplified representation). Electrodes are located along imaginary lines across the head between bony landmarks that intersect at 10% or 20% of their total length distance intervals, hence the "10-20" name. Letters indicate locations according to the brain structure below the electrode. Numbers indicate left-right lateral location, and midline electrodes have the suffix "z": F (Fp1-Fpz-Fp2-F7-F3-Fz-F4-F8), Frontal; C (C3-Cz-C4), Central; T (T3-T4-T5-T6), Temporal; P (P3-Pz-P4), Parietal; O (O1-Oz-O2), Occipital; M (M1-M2), Mastoid. The use of the 10-20 system ensures symmetrical and reproducible electrode placement for within- and between-subject comparisons. A basic sleep recording may be obtained using three electrodes (F4-C4-O2) and one reference electrode (M1).

2. **Electrooculography (EOG)** records changes in voltage induced by the eye rotation, the moving eyeball acting as a small battery, with the retina negative relative to the cornea. Two electrodes located lateral to the eyes allow recording of horizontal eye movements; two other electrodes above and below one eye allow recording vertical movements.

3. E**lectromyography (EMG)** records electrical activity generated by muscle activity. The EMG is typically recorded from under the chin, where muscular tonus changes with sleep stages are most obvious.

Besides EEG, EOG, and EMG, cardiac rhythms (electrocardiogram, or ECG) and respiratory activity can also be recorded simultaneously. Specific wires for EEG, EOG, EMG, ECG, etc., electrodes are

(*Continued*)

Box 1.1 (Continued)

connected through signal amplifiers to systems allowing recording and pre-processing, storing, and reviewing of the signal.

Thanks to the development of computer techniques, early paper-based analog recordings have evolved toward digital polygraphs with high-capacity storage allowing simultaneous recording and on-screen reviewing of multiple channels (up to 256 in high-density EEG). According to the international consensus guidelines (Iber et al., 2007), EEG with 16 or more channels would be an optimum to analyze sleep patterns, although a basic scoring into different stages of sleep can be achieved with a minimum of three derivations located frontally at F4-M1, centrally at C4-M1, and occipitally at O2-M1 (i.e., using right-sided active cortical electrodes F4, C4, O2, and a reference electrode M1 over the left mastoid in the international 10-20 system; see Information Figure 1.1). Equally acceptable alternative derivations are Fz-Cz, Cz-Oz, and C4-M1. In addition, many sleep units have a video camera located in the bedroom, allowing the observation of the patient's sleeping behavior in relation to variations in polysomnography recording, which is particularly useful in the investigation of sleep-related disorders.

Table 1.1 Summary of the main features of each sleep stage

Stages	EEG (Frequency—Hz)	(Amplitude—μV)	Waveform type	Characteristics
AWAKE	14–40	10–30	β	State of full consciousness characterized by a desynchronized EEG pattern of high beta frequency waves of low amplitude.
SLEEP ONSET OR PRE-SLEEP	8–12	20–40	α	Quiet or resting state characterized by posterior alpha rhythm (especially over the occipital cortex) with a lower frequency (8–12 Hz) and increased synchrony and amplitude (20 to 40 μV).
N1	3–7	50–100	θ	Transition period with little or no body movement characterized by the diminution of alpha waves and the appearance of theta waves, slower in frequency (3 to 7 Hz) and greater in amplitude (50 to 100 μV) than alpha waves.
N2 or Light sleep	11–16	50–150	Occasional "sleep spindles" (σ) Occasional K-complexes	Basal oscillations below 5 Hz called "slow waves" on which are periodically superimposed sleep spindles (short-lasting, waxing and waning oscillations in the 11–16 Hz frequency range) and K-complexes (negative sharp waves immediately followed by a positive component standing out from the background EEG with a total duration at least equal to 0.5 second).
N3 or Slow-Wave Sleep (SWS)	0.5–2 (previously 0.5–4) <1	<75 >140	Slow waves (previously δ)	The deepest possible state of physical rest. SWS is characterized by high-amplitude slow oscillations in the 0.5–2 Hz frequency range, maximally expressed at frontal locations. Slow oscillations (<1 Hz) are cortical oscillations occurring during NREM sleep. These slow rhythms play a major role in the synchronization of other NREM sleep oscillations and events (e.g., spindles).
REM or Paradoxical sleep	15–30	<50		Desynchronized EEG activity close to that recorded during wakefulness, characterized by low amplitude-mixed frequency (15–30 Hz, <50 μV) EEG background, rapid eye movements, and muscular atonia.

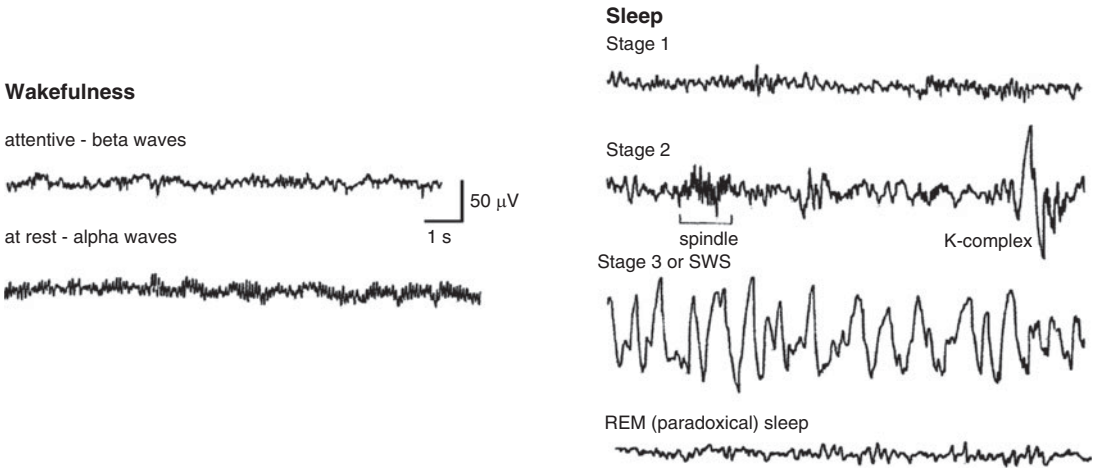


Fig. 1.3 EEG patterns of vigilance states.

NREM sleep stage N2

During stage N2, also known as light NREM sleep, eye movements cease, heart rate slows down, and body temperature decreases, preparing the body to enter deep sleep. Background EEG oscillations decrease below 5 Hz in the delta (δ) range (1–4 Hz). Superimposed on slow oscillations are periodical, transient EEG events named sleep spindles and K-complexes (Figure 1.3). Spindles are short-lasting (0.5–3 seconds), waxing and waning oscillations in the sigma (σ) range (11–16 Hz), whose maximal amplitude is mostly found over central regions (Borbély et al., 2000; De Gennaro, Ferrara, & Bertini, 2000; McCormick, Nielsen, Nicolas, Ptito, & Montplaisir, 1997). Behavioral, electrophysiological (De Gennaro & Ferrara, 2003), and neuroimaging (Schabus et al., 2007) data further suggest a functional differentiation and distinct neuroanatomical bases for slow (11–13 Hz) and fast (13–15 Hz) spindles. The K-complexes are graphoelements characterized by a negative sharp wave of high amplitude immediately followed by a positive component standing out from the background EEG, with a total duration equal to at least 0.5 second. Because of their morphology and duration, K-complexes are sufficiently distinctive and no amplitude criterion is needed (Borbély et al., 2000). K-complexes are optimally recorded at frontal electrodes (e.g., F4 or Fz). Stage N2 should be persistently scored in the absence of K-complexes or spindles until a transition to stage N3 or REM sleep, or the occurrence of a major body movement followed by slow eye movements or an arousal.

NREM sleep stage N3 or SWS

N3 is the deepest stage of NREM sleep, also called slow-wave sleep (SWS), which can be scored when slower waves in the 0.5–2 Hz frequency range represent at least 20% of the 30-second EEG epoch. Because the cut-off was previously set at 4 Hz for the superior limit of slow waves, which may raise confusions with delta activity, revised guidelines strongly discourage the use of the term "delta waves" (e.g., in the 1–4 Hz range) to describe SWS (Silber et al., 2007). Usually, slow waves are maximally expressed at frontal sites (Happe et al., 2002), as well as K-complexes. N3 being the deepest stage of sleep, arousal thresholds are very high, with a longer period of sleep inertia after awakening and possible post-awakening confusion or disorientation (also known as "sleep drunkenness").

REM sleep

Contrary to NREM stages, REM sleep is characterized by the presence of desynchronized, rapid, low-amplitude EEG activity visually close to that recorded during wakefulness, hence its other name of "paradoxical" sleep (Jouvet, Michel, & Courjon, 1959). Five main features determine REM sleep: low amplitude-mixed frequency (15–30 Hz, <50 μV) EEG background, rapid eye movements, muscular atonia, and breath/cardiovascular irregularity. Rapid eye movements (REMs) are conjugate, irregular, and sharply peaked eye movements with an initial deflection usually lasting less than 500 milliseconds. Presence of sawtooth waves or transient muscle activity (phasic twitches) is strongly supportive

evidence, especially when one or more of the basic features are equivocal. During the first REM period of the night, one may observe interspersed K-complexes or sleep spindles, but in the presence of unequivocal REMs these epochs should be scored as REM sleep until there is a transition to stage W, N2, or N3; manifestations of arousal; or major body movements followed by slow eye movements.

The phylogenesis of sleep

Alternation between activity and sleep-like resting states has been found across all studied animal species up to now, although physiological and neurophysiological characteristics may largely differ. The universality of sleep-like resting states suggests an important functionality (or most probably a series of important functionalities) that has/have built up with evolution, hence the paramount importance to explore the phylogenesis of sleep. Furthermore, even though sleep appears to be a universal phenomenon, studies conducted in insects, amphibians, reptiles, avians, mammals, etc., suggest that the differentiation between NREM and REM sleep states, typical of mammalians and birds, is not present—or at least cannot be convincingly disclosed—in all branches of the evolutionary tree, raising supplementary questions about the complementary role of our two main states of sleep in evolution. Even if a logical scheme has not yet been clearly disclosed and adaptations have occurred in some species, studying sleep in the animal kingdom should eventually allow us to understand the phylogenetic characteristics of sleep and target its essential components.

As a word of caution, a major caveat when comparing species is that similar levels of investigations are not always available. On the one hand, sophisticated intracerebral recordings obtained in cats and rodents are available only in exceptional circumstances in humans (e.g., during presurgical recordings) due to their invasive character. On the other hand, polysomnographic recordings (EEG, EMG, and EOG) in animals usually must be carried out in laboratory settings, hence preventing their observation in the natural environment, potentially biasing the results. Although modern telemetric recording techniques now make it possible to equip the animal with a wireless signal transmitter, allowing recording in more natural settings, these are not yet generalized and well adapted to all species. Therefore, many species have been mostly studied at the behavioral level, which limits the scope of possible comparisons.

Sleep or "close to sleep" states in insects

Insects have a daily rhythm of rest and activity. It is not merely due to the influence of the dark–light cycle since it continues being observed even when time synchronizers (also named "zeitgebers") are removed from the environment. Evidence of a close-to-sleep state in insects has long been mostly behavioral. For instance, it has been found that the scorpion adopts a specific position where the body and the head rest flat on the ground, whereas in the bee the antennae are folded up against the head (Tobler & Neuner-Jehle, 1992). Still, because mere observation cannot easily delineate boundaries between sleep and quiet wakefulness in insects, presence of a sleep-analogue condition has been further corroborated using the homeostatic sleep pressure criteria. In the fruit fly (*Drosophila melanogaster*), the most studied kind given its relative simplicity, a homeostatically regulated sleep state has been observed, which in many respects is similar to sleep in mammals (Hendricks et al., 2000; Huber et al., 2004; Shaw, Cirelli, Greenspan, & Tononi, 2000). Indeed, insects exhibit an increase in the duration of the resting state when prior wakefulness is artificially maintained above usual duration levels of activity, e.g., by moving the insect's container or introducing a congener in its environment (Bell-Pedersen et al., 2005; Huber et al., 2004). Furthermore, genetic mutations affect sleep in drosophila; conversely, sleep affects gene expression (Cirelli & Bushey, 2008). Notwithstanding, although changes in brain electrical activity (Nitz, van Swinderen, Tononi, & Greenspan, 2002) and changes in synaptic markers (Gilestro, Tononi, & Cirelli, 2009) are reliably correlated with activity state, sleep in invertebrates seems to lack the large-scale, slow, synchronous neuronal activity similar to that occurring during mammalian and avian SWS (Cirelli & Bushey, 2008; Hendricks & Sehgal, 2004; van Swinderen & Andretic, 2003).

Activity/inactivity states in vertebrates without thermal regulation

FISH

Although several studies have reported behavioral sleep in fishes (specific resting posture, periods of reduced activity, etc.), few studies have investigated EEG (for a review see Hartse, 1994). In tench (*Tinca tinca*), simultaneous recording was made of the electric activity of the brain, muscles and gills activity, respiratory and heartbeat rates, and reactivity to sensorial stimulations. There was no clear difference between the rapid, low-voltage electrical brain activity during the activity (night) as compared to the

rest (day), nor was it possible to evidence periods of eye movements correlated with vegetative variations (Peyrethon & Dusan-Peyrethon, 1967; Zhdanova, 2006, for similar results in the zebra fish). At variance in the catfish (*Ictalurus nebulosus*), the transition from activity to rest was characterized by an increase in low-frequency activity and spikes (Karmanova & Lazarev, 1978). Additionally, there is no indication that a periodic state similar to paradoxical sleep exists in fishes, besides evidence for a global sleep-like state. Also, it remains a matter of debate whether unihemispherical sleep (see below) exists in constantly swimming fishes, doubts being raised in part by the absence of unilateral eye closure (Kavanau, 1998).

AMPHIBIANS

Available data on sleep in amphibians are scarce (for a review see Hartse, 1994). Some species maintain constant vigilance levels during behavioral rest (e.g., the bullfrog), whereas reactivity to sensorial stimulations decreases in others, e.g., the tree-dwelling frog. Similarly, EEG changes correlated with behavioral sleep have been observed in some species, but not in others. Also, there is no evidence for periods of ocular movements during the quiescent stage in amphibians. Unilateral eye closure has been reported only in the bullfrog (*Rana catesbiana*) (Hobson, 1967), occurring only briefly during respiratory acts and apparently unrelated with behavioral sleep.

REPTILES

Mammals and reptiles are neighbors in evolution, having led many researchers to investigate vigilance states in reptiles. Sleep has been studied using continuous polysomnographic recordings (EEG, EMG, EOG, ECG, respiration) in chelonians (tortoises), crocodilians (alligators and caimans), and saurians (lizards and snakes). Unequivocal signs of sleep are present in reptiles at the behavioral level, associated in most studies with intermittent high amplitude, spikes, and sharp waves in the EEG. At variance, few other studies have reported an association with high-amplitude, low-frequency activity (Warner, Huggins, 1978) or detected any sleep-related changes in the EEG (Walker & Berger, 1973).

Although still controversial, there are convincing arguments to support the hypothesis that high amplitude, spikes, and sharp waves define a reptilian sleep state functionally homologous to the mammalian and avian SWS (Hartse, 1994). Indeed, EEG spikes are associated with the presence of a behavioral sleep state in reptilians, and their density increases after sleep deprivation in chelonian (Flanigan, 1974), iguanid (Flanigan, 1973), and crocodilian reptiles (Flanigan, Wilcox, & Rechtschaffen, 1973), suggesting homeostatic regulation. In vitro (Lorenzo, Macadar, & Velluti, 1999; Lorenzo & Velluti, 2004) and in vivo (Gaztelu, Garcıá-Austt, & Bullock, 1991; Lorenzo et al., 1999) studies in turtles further suggest that sleep-related spikes in reptilians originate in the medial cortex (the anatomical and functional homologous of the mammalian hippocampus; López, Vargas, Gómez, & Salas, 2003), then propagate in the adjacent dorsal cortex.

The lack of high-amplitude, slow waves in reptiles has long been attributed to the absence in these species of the thick six-layered neocortex responsible for generating EEG slow waves in mammals (Hartse, 1994). Alternate hypotheses nowadays propose (a) that the reptilian dorsal cortex lacks the interconnectivity necessary to generate sleep-related slow waves in the electroencephalogram (Rattenborg, 2006, 2007); (b) that the thalamocorticothalamic circuitry is less elaborate in reptiles despite similarities across mammals, birds, and reptiles in the basic neurochemistry, neuroanatomy, and neurophysiology of the thalamic reticular nucleus (Kenigfest et al., 2005; Llinas & Steriade, 2006) involved in the genesis of sleep-related neuronal oscillations in mammals (Steriade, 2006); and/or (c) that differences in the type and/or density of glia (Ari & Kalman, 2008) may explain why reptiles lack SWS (Rattenborg, Martinez-Gonzalez, & Lesku, 2009), given that glia may amplify the effect of corticocortical connectivity on neuronal synchrony during sleep (Amzica & Steriade, 2000).

Regarding REM sleep analogues in reptiles, recorded sleep episodes associated with rapid eye movements and heartbeat variations are very brief (a few seconds) and extremely rare (a few minutes in several weeks of recording) in crocodilians and lizards. The analogy of these episodes with paradoxical sleep is still discussed. Also, the prevalence of unilateral eye closure during behavioral sleep suggests that reptilian sleep may occur unihemispherically (Flanigan et al., 1973; Tauber, Roffwarg, & Weitzman, 1966).

REM and NREM sleep in birds and mammals

Since the discovery of REM sleep as a distinct phase in mammalian sleep, researchers have searched for the origin and causes of the duality between REM and NREM sleep. Because birds and mammals have evolved independently without common reptilian

ancestors, the presence of REM sleep in both suggests that this state has appeared independently in the two phylogenetic branches to fulfill a function essential to more complex brains (Jouvet, 1994), leaving unsolved for now the question of its origins.

SLEEP IN BIRDS

Like mammals, birds have NREM–REM sleep cycles (Campbell & Tobler, 1984; Lesku, Roth, Rattenborg, Amlaner, & Lima, 2009; Rattenborg & Amlaner, 2002). They are also the only taxonomic group other than mammals exhibiting high-amplitude slow waves in the EEG during NREM sleep (Rattenborg et al., 2009), departing from the high-amplitude spikes and sharp waves of reptilian sleep. Although some controversies persist, slow-wave activity during SWS appears to be homeostatically regulated in birds. For instance, SWA increases in pigeons following short-term sleep deprivation (Martinez-Gonzalez, Lesku, & Rattenborg, 2008). It is hypothesized that the confluent evolution of homeostatically regulated SWS in birds and mammals is directly linked to their common evolution toward large, heavily interconnected brains capable of performing complex cognitive processes (Rattenborg et al., 2009).

Adaptative sleep in birds

Like most mammals, birds exhibit bihemispheric NREM and REM sleep in many conditions. However, they have also developed the ability to sleep with one eye open, the contralateral hemisphere being awake to overcome the problem of sleeping in specific situations. Spooner (1964) was first to observe an association between unilateral eye closure and unihemispheric slow-wave sleep (USWS) in young chickens (*Gallus gallus domesticus*). In those, the hemisphere contralateral to the open eye showed EEG activity typical of wakefulness, whereas in the other hemisphere EEG activity was typical of SWS. The fact that birds are able to control which hemisphere can sleep in response to changes in anticipated risks suggests that USWS and unilateral eye closure serve a predator-detection function. Indeed, mallard ducks positioned at the edge of the group during rest (a position perceived by the animals as dangerous (Bednekoff & Ritter, 1994; Elgar, 1989) exhibit a 150% increase in USWS and a strong preference for directing the open eye toward the potential source of danger (Rattenborg, Lima, & Amlaner, 1999), as compared to ducks safely sleeping in the center of the group, who display bihemispheric sleep. Thus, birds not only have the capacity to control unihemispherical sleep, but also use this ability in a manner that reduces the conflict between sleep need and predator detection. Although birds may also use USWS to continuously monitor their environment for other purposes (e.g., food availability, weather variations, etc.), predator detection is likely to be the most important given its surviving value. Additional evidence suggests that some birds use unihemispherical sleep while migrating, allowing sleep while engaged in long overseas travels.

SLEEP IN MAMMALS

Even though mammals represent a small fraction of living species, they have been logically the most thoroughly investigated, humans belonging to this class. Alternating patterns between NREM and REM sleep were found in almost 100 species studied using polysomnographic recordings, suggesting the generality of NREM–REM sleep patterns in mammalians, but few exceptions discussed later (Fuchs, Maury, Moore, & Bingman, 2009).

REM sleep in mammals

Following the discovery of rapid eye movements (REMs) during sleep by Aserinsky and Kleitman in 1953, tentatively linked to dreaming activity, William Dement found in 1957 an association between REMs and distinctive patterns of cortical EEG activity in the sleeping cat, hence the name of REM sleep for this state. At the same time, the French neurobiologist Michel Jouvet, who was investigating subcortical activities in sleeping cats, observed periods of muscle atonia arousing simultaneously with high-voltage spiky waves in the EEG, similar enough to the waking stage (Jouvet & Michel, 1959). The finding was curious and certainly a paradoxical phenomenon, because at that time fast cortical activity was still regarded as the unmistakable electrophysiological sign of wakefulness and muscle atonia as an invariable sign of sleep. This apparent discrepancy led Jouvet (1959) to name this strange state of wake-like brain activity "paradoxical sleep." It was soon recognized that REM and paradoxical sleep were two names for the same phenomenon, which was further studied by Jouvet and others in more than 100 species of vertebrates. Their main conclusion was that this essential phase of sleep exists only among warm-blooded animals.

Outstanding exceptions to standard NREM–REM sleep patterns are archaic monotremes *echidna* and *platypus*, primitive mammals that lay eggs, as birds or reptiles do, and cetaceans (whales and dolphins).

Archaic sleep in monotremes

Most studies investigating mammalian sleep have been performed on eutherians or marsupials, the two main subclasses of mammals. The third subclass is monotremes, found in Australia and New Guinea, whose two living species are echidna and platypus. Fossil and genetic evidence indicate that monotremes diverged from other mammalian lines about 150 million years ago, and that echidna and platypus are derived from a platypus-like ancestor (Clemens, 1989; Flannery, 1989; Westerman & Edwards, 1992). They have more genetic and physiological similarities with reptiles and birds than other mammals and are thought to possess characteristics of the common mammalian ancestor (Grutzner et al., 2004), hence they are considered "living fossil mammals" that may inform us about the evolution of sleep.

Initial studies have suggested that echidna lacks REM sleep (Allison & Van Twyver, 1972), because no typical REM sleep low-voltage EEG pattern is observed at the cortical level like in eutherian and marsupial mammals. However, further investigations have shown that brainstem activity is different from that seen in other mammals during NREM sleep and resembles that seen in REM sleep. Indeed, activity of brainstem neurons decreases like during NREM sleep, but variability increases as during REM sleep (Siegel, Manger, Nienhuis, Fahringer, & Pettigrew, 1996). Since it is known that brainstem neuronal activity generates REM sleep, these results suggest that echidna has a REM sleep-like state, but not accompanied by low-voltage cortical EEG like in other mammals. In the platypus, who was also thought devoid of REM sleep, behavioral observation and telemetric measures have demonstrated atonia with rapid eye movements, twitching, and the electrocardiogram pattern of rapid eye movement, altogether with moderate or high-voltage cortical EEG typical of NREM sleep and REM-like brainstem neuronal activation during 6–8 hours a day, actually proposing the platypus as a champion of REM sleep (Siegel et al., 1999). These results in monotremes suggest that low-voltage electroencephalogram and cortical desynchronization are more recently evolved features of mammalian REM sleep, which may have had its precursor state in reptilian species (Siegel et al., 1999).

The evolving sleep of marine mammals

In their book *The Promise of Sleep*, Dement & Vaughan (1999) notice that the dolphin, originally a land mammal that has returned to the sea, maintains a number of terrestrial traits, including bearing live offspring and, unlike fish, breathing air. At variance with terrestrial mammals, however, breathing is under voluntary control in cetaceans—a process that should preclude sleep. In order to solve what seems an impossible equation, cetaceans have therefore opted for unihemispherical sleep (Figure 1.4), allowing one half of the brain to go to sleep while the other half remains awake (Lyamin, Manger, Ridgway, Mukhametov, & Siegel, 2008; Siegel, 2005). Thus, high-voltage slow waves almost never occur in both hemispheres at the same time, with the eye contralateral to the hemisphere with slow waves being closed while the other eye remains open (Lyamin, Mukhametov, & Siegel, 2004; Mukhametov, Lyamin, Chetyrbok, Vassilyev, & Diaz, 1992; Mukhametov, Supin, & Polyakova, 1977).

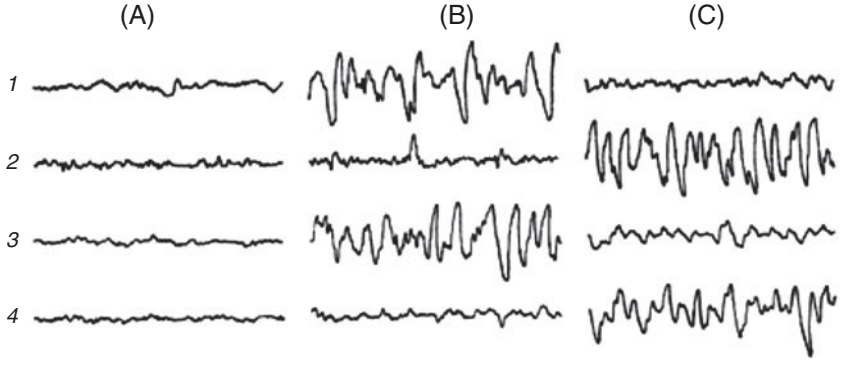


Fig. 1.4 EEG recording in a bottlenose dolphin during waking (A) and unihemispheric slow-wave sleep (USWS) in the right (B) and left (C) hemispheres (1: right cortex; 2: left cortex; 3: right thalamus; 4: left thalamus). Modified from Supin & Mukhametov, 1986.

Unihemispherical SWS (USWS) may also serve additional functions like efficient predator monitoring in the environment and thermogenesis, which has most likely been important in the evolution of USWS in cetaceans but also for their apparent lack of REM sleep (Lyamin et al., 2008). Indeed, no REM sleep episodes have been detected in any of the four species examined by Mukhametov and colleagues (Lyamin et al., 2002; Mukhametov, 1984, 1995; Mukhametov, Oleksenko, & Poliakova, 1988; Mukhametov et al., 1977), despite long periods of electrophysiological recording, making cetaceans the only studied mammals in which REM sleep seems to be totally inexistent, at least when accounting for the unusual form of REM sleep in monotremes. Only one published study has reported EEG features of REM sleep with marked loss of tonus of trunk muscle in a pilot whale, but for no more than 6 minutes and one time only out of three nonconsecutive nights (Shurley, Serafetinides, Brooks, Elsner, & Kenney, 1969). USWS has been observed in only three aquatic orders (e.g., Cetacea, Pinnipedia, and Sirenia) among mammals. In cetaceans, virtually all of their sleep is of USWS type, whereas eared seals and manatees may also display bihemispheric SWS (BSWS) and REM sleep (Rattenborg, Amlaner, & Lima, 2000).

Unlike the terrestrial environment, there are few warm, safe places to sleep in the ocean. This may explain why, contrary to all terrestrial mammals, killer whales (*Orcinus orca*) and dolphins have minimal amounts of sleep behavior (e.g., immobility or eye closure) at birth, slowly increasing to adult levels over months. It may allow the neonate to thermoregulate in cold ocean water and to be protected during development while swimming with its mother. As the animal gains mass and blubber and approaches adult size, adult-like sleep behavior emerges, including periods of immobility. The mother also presents a near absence of typical sleep behavior during the postpartum period (Siegel, 2005), for periods that greatly exceed those of sleep deprivation reported to kill rats (Rechtschaffen, 1998). Interestingly, neither mother nor calf seems to exhibit a rebound in the amount of sleep behavior after this period, questioning the presence of homeostatic regulation in cetacean sleep. Still, some evidence has been observed in one study for a rebound after experimental deprivation of slow waves, but responses were highly variable among animals (Oleksenko, Mukhametov, Polyakova, Supin, & Kovalzon, 1992). Besides differences in recording methods, the peculiar properties of cetaceans' sleep (e.g., USWS combined with lack of typical motor and sensorial inactivity and apparent lack of homeostatic regulation) are questioning the very nature of the essential constituents of sleep. Further investigations are necessary to determine which, if any, neurochemical and neurophysiological aspects of sleep, besides unilateral neocortical slow waves and eye closure, are preserved in cetaceans and might constitute the core substance of sleep (Manger, Ridgway, & Siegel, 2003).

Neurobiology of sleep

Initiation and control of sleep–wake cycles and alternation between sleep states are regulated by activity in specific neuronal populations located in two broad regions, namely the basal forebrain and hypothalamus. Before describing their mode of action, it is first necessary to review the neurochemical systems that promote cerebral arousal and prevent the organism from falling asleep (Figure 1.5), allowing further understanding of the basic mechanisms of sleep initiation and maintenance (Datta & Maclean, 2007). Over the past decades, a large set of neurochemical-specific wake-promoting cells have been identified within the ascending activating system (AAS) in the reticular formation, namely acetylcholine, histamine, norepinephrine, serotonin, hypocretin/orexin, dopamine, and glutamate. Dorsal projections from these pontine and midbrain wake-promoting cells activate thalamocortical systems, whereas ventral projections activate hypothalamocortical and basocortical systems (Garcia-Rill, 2002).

Acetylcholine

(Ach)-synthesizing cholinergic cells are located mostly in the pedunculopontine tegmentum (PPT) of the brainstem and in the anterior hypothalamus (AH) of the basal forebrain (BF). Activity in these neuronal groups is high during wakefulness (maximally active in the basal forebrain) and REM sleep, and strongly diminished during NREM sleep (minimally active for PPT cholinergic cells). From a functional point of view, PPT and BF cholinergic cells are part of the main arousal systems in the brainstem and forebrain, respectively. These neuronal populations are causally involved in the generation of the desynchronized EEG pattern in both wake and REM sleep stages (Datta & Maclean, 2007; Steriade, Pare, Datta, Oakson, & Curro Dossi, 1990) by releasing acetylcholine in the diencephalon, hence blocking oscillatory discharges of thalamic mechanisms responsible for EEG spindles and slow waves (McCormick, 1989;

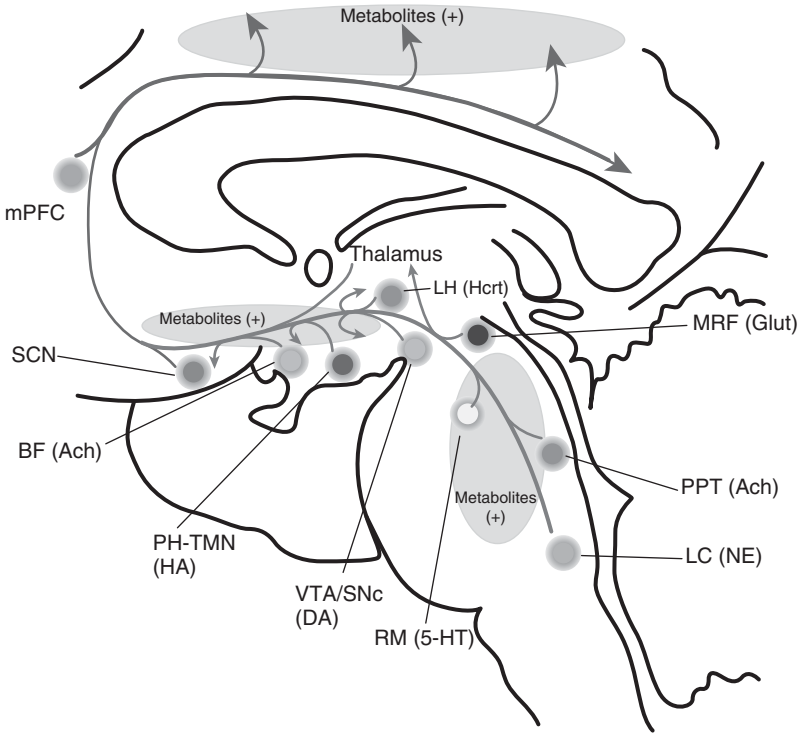


Fig. 1.5 Sagittal view of human brain depicting the main neurotransmitter structures and pathways involved in the generation and maintenance of sleep and wakefulness. Acetylcholine (Ach)-synthesizing (cholinergic) cells in the pedunculopontine tegmentum (PPT) and in the anterior hypothalamus (AH) of the basal forebrain (BF). (HA)-synthesizing histaminergic cells in the posterior hypothalamic tuberomammillary nucleus (PH-TMN). Norepinephrine (NE)-synthesizing (noradrenergic) cells in the locus coeruleus (LC). Serotonin (5-HT)-synthesizing (serotonergic) cells in the raphe nuclei (RN). Hypocretin-orexin cells in the lateral hypothalamus (LH). Dopamine (DA)-synthesizing dopaminergic cells in the substantia nigra compacta (SNc) and ventral tegmental area (VTA). (Glut)-synthesizing glutamatergic cells in the mesencephalic reticular formation (MRF). From Datta & MacLean (2007).

Steriade, McCormick, & Sejnowski, 1993). Although sharing many properties, these two clusters of cholinergic cells also present the following specific features.

CHOLINERGIC CELLS IN THE PEDUNCULOPONTINE TEGMENTUM

The pedunculopontine tegmentum (PPT) nucleus, being one of the major aggregations of cholinergic neurons in the mammalian brainstem, promotes wakefulness by activating thalamocortical, hypothalamocortical, basocortical, suprachiasmatic, and amygdaloid wake-promoting systems of the forebrain (Datta, 1995; Datta & Siwek, 1997). Bursting discharges of a subgroup of these PPT neurons are also involved in generation of pontogeniculooccipital waves (PGO; see below). Additionally, some PPT neurons selectively active during REM sleep participate in the suppression of muscle tone, preventing motor activity during this stage of sleep (Datta & Maclean, 2007; Lyamin et al., 2008).

CHOLINERGIC CELLS OF THE BASAL FOREBRAIN

Cholinergic cells in the basal forebrain (BF) play an important role in hippocampal and neocortical activation (Detari, Juhasz, & Kukorelli, 1984; Detari & Vanderwolf, 1987; Nunez, 1996; Stewart, MacFabe, & Vanderwolf, 1984). They receive input from other brainstem and hypothalamic wake-promoting systems and, in turn, have widespread projections to the cerebral cortex (Detari & Vanderwolf, 1987; Fisher, Buchwald, Hull, & Levine, 1988; Gritti, Mainville, Mancia, & Jones, 1997; Zaborszky, Carlsen, Brashear, & Heimer, 1986a; Zaborszky, Cullinan, & Braun, 1991;

Zaborszky, Heimer, Eckenstein, & Leranth, 1986b). BF cholinergic cells are widely involved in wake-promoting behaviors, including attention, sensory processing, and learning (Datta & Maclean, 2007).

Histamine

(HA)-synthesizing histaminergic cells are located in the posterior hypothalamus (PH), especially the tuberomammillary nuclei (TMN). PH-TMN neurons are involved in promoting and maintaining wakefulness (John, Wu, Boehmer, & Siegel, 2004), sending projections through wake-promoting structures in the brainstem and forebrain (Brown, Stevens, & Haas, 2001; Hass & Panula, 2003; Huang et al., 2001; Inagaki et al., 1988; Lin, Luppi, Salvert, Sakai, & Jouvet, 1986; Panula, Pirvola, Auvinen, & Airaksinen, 1989; Sakai, El Mansari, & Jouvet, 1990; Sherin, Elmquist, Torrealba, & Saper, 1998). Single cell recordings in freely moving cats and rats show that the majority of TMN histaminergic neurons are active during wakefulness and silent during sleep (Ko, Estabrooke, McCarthy, & Scammell, 2003; Sakai et al., 1990; Takahashi, Lin, & Sakai, 2006; Vanni-Mercier, Sakai, & Jouvet, 1984). Conversely, PH lesions produce a comatose-like continuous sleepiness (Saper, Chou, & Scammell, 2001). Cessation of histaminergic activity may be related to the loss of consciousness during sleep (John et al., 2004).

Norepinephrine

Most (NE)-synthesizing noradrenergic cells are located in the locus coeruleus (LC) of the pons. They project directly to the cerebral cortex, hippocampus, amygdala, and other subcortical areas such as the thalamus, hypothalamus, and BF (Berridge & Waterhouse, 2003; Dahlstrom & Fuxe, 1964; Datta & Maclean, 2007; Lewis, 1987). During wakefulness, noradrenergic neurons have a regular and tonic firing, slowing down during the initial phase of SWS (Aston-Jones & Bloom, 1981b; Foote, Bloom, & Aston-Jones, 1983). Like histaminergic cells, they are inactive during REM sleep (Datta & Maclean, 2007). Cessation of activity in noradrenergic cells during sleep seems to be related to loss of muscle tone (John et al., 2004; Lai, Kodama, & Siegel, 2001). Activation/inactivation of locus coeruleus neurons results in an increase/decrease of wakefulness, respectively (Berridge & Foote, 1991; Berridge, Page, Valentino, & Foote, 1993), suggesting that activation of noradrenergic cells participates in the process of cortical activation and behavioral arousal.

Serotonin

Serotonergic (5-HT)-synthesizing cells are located in cluster nuclei, called raphe nuclei, in the brainstem. The two main clusters are the *rostral* cluster (a midbrain/pontine group sending projections to the telencephalic hemispheres) and the *caudal* cluster (a medullar group sending projections to the spinal cord) (Lyamin et al., 2008). Serotonergic cells have a similar discharge pattern (maximal firing during wakefulness, decreased firing during SWS, no firing during REM sleep (Lydic, McCarley, & Hobson, 1983; McGinty & Harper, 1976) and project almost to the same brain regions as noradrenergic cell projections (Morgane, Galler, & Mokler, 2005; Tork, 1990; Vertes & Martin, 1988). Unlike noradrenergic cells, however, their role in promoting sleep and/or wakefulness remains unclear (Datta & Maclean, 2007). It has been proposed that serotonin may play a role in maintaining arousal and regulating muscle tone and some phasic events of REM sleep (John et al., 2004; Wu, Gulyani, Yau, et al., 1999; Wu, John, Boehmer, et al., 2004). On the other hand, a lesion in the raphe nuclei increases wakefulness and suppresses SWS (Sakai & Crochet, 2001), suggesting that serotonergic neurons are involved in SWS promotion. Pharmacological studies also suggest that serotonin may suppress activity of hypothalamocortical and basocortical wake-promoting systems (Cape & Jones, 1998; Khateb Fort, Alonso, Jones, & Muhlethaler, 1993). Another, nonexclusive functional hypothesis is that tonic activity of serotonin during waking tends to suppress phasic events, and during REM sleep allows high-voltage bursts of electrical activity and the generation of the PGO (Siegel, 2000).

Hypocretin/orexin

Hypocretinergic or orexinergic neurons, recently causally linked to sleep, are located in the lateral hypothalamus, between the sleep-activator neurons of the anterior hypothalamus (GABAergic cells, see below) and the wake-activator histamine neurons of the posterior hypothalamus (Gerashchenko & Shiromani, 2004). Hypocretinergic cells promote wakefulness by their strong projections toward many primary wake-promoting neuronal systems of the brain (Gerashchenko & Shiromani, 2004; Siegel, 2004). Loss of these hypocretin/orexin cells is linked to human narcolepsy (Overeem et al., 2002; Thannickal, Siegel, & Moore, 2003).

Dopamine

At variance with other wake-promoting neurotransmitters described above, (DA)-synthesizing dopaminergic

cells located in the substantia nigra compacta (SNc) and the ventral tegmental area (VTA) present a similar pattern of activation across sleep–wake states (Steinfels, Heym, Strecker, & Jacobs, 1983; Trulson & Preussler, 1984; Trulson, Preussler, & Howell, 1981). Notwithstanding, extracellular concentrations of dopamine are significantly increased during wakefulness periods (Feenstra, Botterblom, & Mastenbroek, 2000; Trulson, 1985).

Glutamatergic cells

Glutamatergic cells are located in the mesencephalic reticular formation (MRF). They send strong projections to thalamic nuclei and the hypothalamus, thereby activating the thalamocortical and hypothalamocortical networks, respectively (Datta & Maclean, 2007). Noninvasive neuroimaging techniques in human subjects have shown that MRF activity is higher during wakefulness than during SWS (Braun et al., 1997; Kajimura et al., 1999; Maquet et al., 1990), in line with the proposal that glutamatergic neurons are involved in the maintenance of behavioral states of wakefulness (Datta & Maclean, 2007). Like histaminergic neurons of the posterior hypothalamus, electrolytic lesions in the mesencephalic reticular formation region may cause a comatose-like continuous sleepiness (Saper et al., 2001).

Generation and maintenance of NREM sleep

For one part, sleep initiation results from the decreasing power of wake-promoting brain neurons. NREM sleep generation and maintenance also depend on the implication of four types of molecules: adenosine, prostaglandin, cytokine, and most importantly inhibitory amino acid (GABA). Already in 1930, von Economo demonstrated the existence of a sleep-promoting area in the brain by showing a correlation between severe insomnia and damage to the anterior hypothalamus. A few decades later, GABAergic neurons (also named "NREM-on cells," see below) were identified in the ventrolateral preoptic (VLPO) area of the hypothalamus. GABA cells are unique because, by contrast to most neurons, they are maximally active during NREM sleep, less active during REM sleep, and minimally active during wakefulness (Siegel, 2004; Szymusiak, 1995; Szymusiak, Steininger, & McGinty, 2001). In this respect, GABAergic neurons may be viewed as the most potent sleep-promoting component of the brain. Additionally, bursting activity of GABAergic cells in the VLPO abolishes transmission of incoming signals to the cortex, by inhibiting serotonergic and noradrenergic activity of the brainstem, but also in histaminergic and cholinergic systems, two major arousal systems in the brain. By this way, continuous GABA release suppresses activity in wake-promoting areas and activates NREM sleep (Datta & Maclean, 2007; Nitz & Siegel, 1997a; Nitz & Siegel, 1997b; Siegel, 2005). Slow-wave sleep (SWS), which characterizes deep NREM sleep, emerges by the reduction of neuronal activity in wake-promoting brain regions due to the activation of GABAergic cells in the preoptic area, which in turn induces SWS. GABAergic inhibitory function is facilitated by increased synthesis of the growth hormone-releasing hormone (GHRH), also involved in increasing the depth and duration of SWS (Krueger & Obal, 2003; Obal & Krueger, 2004).

Adenosine may play a role in the homeostatic regulation of sleep. Indeed, sleep duration and depth are modulated by adenosine concentration in the basal forebrain cholinergic region. Adenosine level progressively increases during extended waking periods and slowly declines during recovery sleep. It is hypothesized that increased adenosine concentration in the cholinergic basal forebrain would decrease EEG arousal, increase drowsiness, and promote EEG delta wave activity during subsequent NREM sleep (Porkka-Heiskanen et al., 1997). Additionally, adenosine may play a role in interindividual variability in sleep structure, NREM sleep intensity, and detrimental effects of sleep loss on neurobehavioral performance in humans (Landolt, 2008). The exact biochemical mechanisms underlying the effects of adenosine on NREM sleep homeostasis remain a hotly debated topic (for further discussion, see Siegel et al., 2006).

Generation and maintenance of REM sleep

As compared to NREM sleep, mechanisms involved in REM sleep generation and maintenance are much more complex. In their pioneering study, Jouvet and colleagues (Jouvet, 1962; Jouvet & Michel, 1959, 1960) showed periodic occurrence of REM sleep signs (REMs, muscle atonia, etc.) in a pontine preparation (i.e., transection just above the midbrain-pontine junction), demonstrating that REM sleep generation originates from the brainstem. Further studies have tried to provide a more detailed picture of the REM sleep controlling network. They have shown that REM signs are controlled by specific neurons, called *effector neurons*, and concentrated for the most part in the reticular formation (RF) of the pons (McCarley, 2007; Steriade & McCarley, 2005). Generation and

maintenance of REM sleep involve a complex system of neuronal connections between effector neurons, a system regulated by ratios of aminergic and cholinergic neurotransmitters.

In 1975, McCarley and Hobson published the reciprocal interaction model to explain the mechanisms of REM sleep. They proposed that REM sleep generation and maintenance depend on reciprocal interactions between so-called "REM-on" and "REM-off" groups of cells (Figure 1.6) (McCarley & Hobson, 1975). REM-on neurons are reticular cholinergic cells located in the pedunculopontine tegmentum (PPT) and lateral dorsal tegmentum (LDT) of the brainstem. REM-off cells are monoaminergic (serotonergic and noradrenergic) neurons located in the locus coeruleus (LC) (El Mansari, Sakai, & Jouvet, 1989; Thakkar, Strecke, & McCarley, 1998). During wakefulness and NREM sleep, high levels of activity in REM-off aminergic neurons actively inhibit the action of cholinergic REM-on neurons. Throughout NREM sleep, however, activity in REM-off aminergic cells gradually decreases, eventually releasing inhibition on REM-on cells, whose increased activity will in turn induce REM sleep (Brown & McCarley, 2008). Additional evidence suggests that REM-on cells have an excitatory effect on REM-off cells during REM sleep, which will terminate the REM sleep phase when a sufficient level of activity has been attained as to inhibit again activity in REM-on cells (McCarley & Hobson, 1975). Brainstem PPT/LDT cholinergic neurons are promoters of REM sleep by sending excitatory cholinergic projections to the effector neurons. For instance, they cause loss of muscle tone during REM sleep by triggering simultaneous inhibition of and withdrawal of excitation to motoneurons. When these neurons are artificially activated (e.g., by microinjection of acetylcholine agonists into specific regions of the pons), prolonged REM sleep periods are elicited, further showing their crucial role in the regulation of REM sleep itself (Coleman, Lydic, & Baghdoyan, 2004).

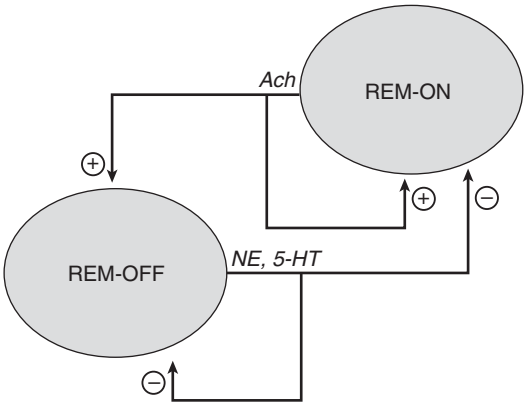


Fig. 1.6 The reciprocal inhibition model for REM sleep (McCarley & Hobson, 1975). During wakefulness and NREM sleep, noradrenergic (NE) and serotonergic (5-HT) activity inhibits cholinergic (Ach) REM-on neurons in the pedunculopontine tegmentum (PPT) and lateral dorsal tegmentum (LDT). Throughout the course of a NREM sleep episode, inhibitory feedback gradually decreases NE and 5-HT activity in the locus coeruleus and dorsal raphe nucleus (5-HT), respectively, releasing inhibition on acetylcholine REM-on cells, whose increased activity induces REM sleep. Activity in REM-on cells in turn exerts an excitatory effect on REM-off cells during REM sleep, eventually leading to the termination of REM sleep when a sufficient level of inhibitory activity has been attained in NE and 5-HT REM-off cells.

Sleep neurophysiology

Three regions are known to play a main role in the generation and maintenance of sleep stages and their distinguishing features (e.g., spindles or pontogeniculooccipital waves): (i) the thalamus, including nuclei such as the thalamic reticular nucleus sending and receiving projections to and from the cortex; (ii) the hypothalamus, located behind the thalamus; and (iii) the reticular formation, located throughout the pons and mesencephalon, sending projections to the neocortex through thalamic nuclei (Marieb, 1999).

Whereas neurobiological investigations have been conducted mostly at the cellular level in animals, the neurophysiological study of sleep and the macroscopic delineation of sleep-related cerebral structures have also been achieved in humans using noninvasive neuroimaging and electrophysiological approaches. In this respect, positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques have contributed to the identification of the cortical and subcortical functional neuroanatomical networks involved in sleep and its components. The spatial accuracy of these techniques (up to a few millimeters in resolution) is complementary to the high temporal resolution, at the millisecond scale of neuronal transmission, of electrophysiological techniques that are playing a fundamental role in the investigation of temporal patterns of neuronal synchronization oscillatory rhythms using, e.g., EEG (Happe et al., 2002), high-density EEG (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Riedner et al., 2007), or magnetoencephalography (MEG; Ioannides et al., 2004) during both REM and NREM sleep. Optimal combinations of these techniques (e.g., simultaneous EEG-fMRI, see below for instance

Dang-Vu et al., 2008; Schabus et al., 2007) and their intrinsic advantages minimize their respective drawbacks, providing important information on the physiology of sleep and its regulation.

In this section, we will offer a description of the cerebral networks implicated in a permissive and/or executive manner in NREM and REM sleep stages. This neurophysiological macroscopic level of description will be linked with a summary description of the cortical and subcortical cellular and synaptic interaction processes thought responsible for these cerebral patterns and their respective implication in the generation of sleep stages and their specific features. All studies presented in this section refer to "canonical sleep," e.g., normal sleep in healthy young humans, without any associated pathology or interferences due to prior sleep deprivation or pharmacological intervention that are beyond the scope of this chapter.

NREM sleep

As discussed above, there is a progressive change from wakefulness to NREM sleep in the way neuronal populations fire, from a desynchronized tonic mode toward bursting synchronous activity. Self-sustained oscillatory activity in thalamic nuclei initiates a cascade of neurophysiological events, eventually leading to the large-scale synchronization of cortical neuronal populations responsible for the low-frequency, high-amplitude EEG typical of NREM sleep. As illustrated in Figure 1.7, three interconnected neuronal populations are involved in the generation of NREM sleep oscillations: (i) corticothalamic neurons (neurons A) that have excitatory synapses on thalamocortical neurons and thalamic reticular neurons; (ii) thalamocortical relay neurons (neurons B) with their cell bodies in the thalamus and axons making excitatory synapses on pyramidal neurons in the cerebral cortex and on neurons in the thalamic reticular nucleus; and (iii) thalamic reticular neurons (neurons C) located in the reticular thalamic nuclei and forming inhibitory synapses on thalamocortical neurons. Neurons A and B are excitatory glutamatergic neurons, whereas neurons C are GABAergic inhibitory neurons. The resulting loops into the corticothalamocortical network are involved by different ways in the generation of spindles and delta waves, which

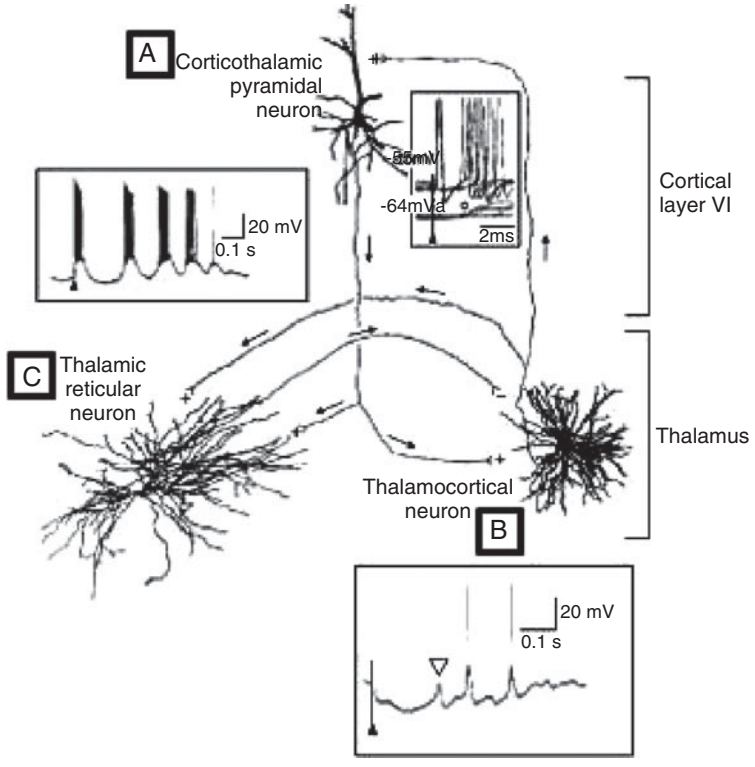


Fig. 1.7 Neuronal loops in corticothalamic networks involved in generating the coherent low-frequency oscillations characteristic of NREM sleep (spindles, delta, and slow oscillations). [A] corticothalamic neurons; [B] thalamocortical relay neurons; [C] thalamic reticular neurons. From Borbély et al., (2000).

in turn are organized by cortically generated slow oscillations (<1 Hz; Steriade, 2001). Altogether, these rhythms are produced by a "unified oscillatory machine" encompassing thalamic and cortical structures, under the control of brainstem and forebrain modulatory systems, and are coalescent within specific time windows corresponding to the depolarizing phase (up state) of the slow oscillations (Steriade, 2006).

NEURAL CORRELATES OF SLOW OSCILLATIONS IN NREM SLEEP

A consequence of large-scale neuronal synchronization is that coincident bursts of activity are followed by equally synchronous depolarization periods (down state), during which neurons are virtually silent. When cerebral activity is recorded and averaged over long periods, for tens of seconds up to minutes as is the case with PET scanning, it entails that areas in which activity is most synchronous will be those in which regional cerebral blood flow (CBF) will be most decreased due to the fact that averaging has included the long depolarization periods during which energy demands are minimal (Maquet, 2000). Accordingly, PET studies have consistently reported decreased regional CBF and oxygen consumption during NREM sleep, as compared to wakefulness or REM sleep, in a set of subcortical and cortical regions encompassing the dorsal pons and the mesencephalon, cerebellum, thalamus, basal ganglia, basal forebrain, anterior hypothalamus, neocortical prefrontal and anterior cingulate cortices, and precuneus and mesial parts of the temporal lobe (Figure 1.8) (Andersson et al., 1998; Braun et al., 1997; Kajimura et al., 1999; Maquet, 2000; Maquet et al., 1997). The relationship between the depth of NREM sleep and decreased rCBF thought to reflect increased synchronization is further confirmed by correlations between increased EEG spectral power for slow oscillations in the delta (1–4 Hz) range and decreased rCBF in most of the cortical regions reported above, particularly in medial prefrontal regions where response to homeostatic sleep pressure is prominent (Dang-Vu et al., 2005).

Above rCBF patterns reflecting synchronous activity within specific brain areas, more recent studies have taken advantage of the better temporal resolution of fMRI (about one second) combined with simultaneous EEG recordings to highlight transient changes in regional cerebral activity specifically associated with slow (<1 Hz; >140 μV) and delta waves (0.5–4 Hz; 75–140 μV) during NREM sleep (Dang-Vu et al., 2008). Using an endogenous event-related approach, these authors searched for

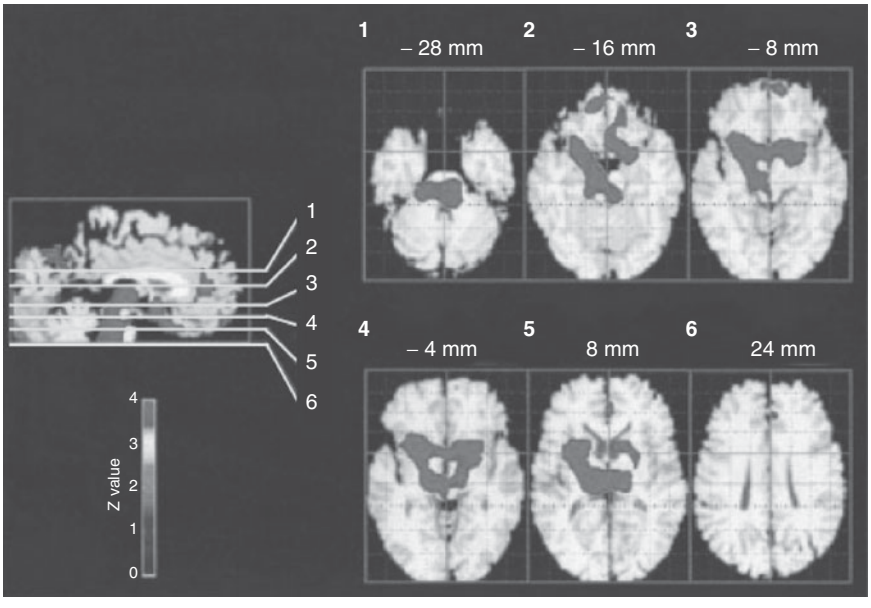


Fig. 1.8 Brain areas in which regional CBF (rCBF) decreases during NREM sleep as compared to wakefulness and REM sleep, measured using PET. Mid-sagittal (left panel) and transverse (right panel) sections show higher synchronization (as reflected by decreased rCBF) in central core structures (brainstem and thalamic nuclei), basal forebrain, basal ganglia, anterior hypothalamus, orbitofrontal and anterior cingulate cortices, and precuneus. Numbers in the left panel refer to the corresponding transverse sections on the right. From Maquet et al. (1997).

brain regions in which changes in activity (i.e., blood oxygen level-dependent [BOLD] responses in fMRI) were coincident with the active depolarized ("up") state of these oscillations, as indexed by peak negativity in the EEG. Results show that increased cerebral activity is associated both with slow and delta waves in several cortical areas, including the inferior frontal and medial prefrontal cortices and the precuneus and posterior cingulate areas. Besides these commonalities, however, slow oscillations (<1 Hz) are associated with increased activity in the parahippocampal gyrus, the cerebellum, and the brainstem, whereas delta waves are specifically associated with increased activity in frontal areas (Figure 1.9).

Additionally, Dang-Vu et al. (2008) found increased activity associated with slow oscillations in the midbrain and the pontine tegmentum, a region that includes critical structures involved in the regulation of sleep and wakefulness (especially cholinergic and aminergic nuclei; see above), the activation encompassing the noradrenergic locus coeruleus (LC). This unexpected result suggests that these structures are active in phase with slow oscillations, perhaps allowing the brain to periodically restore microwake-like activity patterns in order to facilitate neuronal interactions. Taken together, these results further confirm that SWS is not, as may have been thought, a state of brain quiescence, but genuinely is an active state during which phasic increases in brain activity are synchronized to slow oscillations (Dang-Vu et al., 2008).

FUNCTIONAL NEUROANATOMY OF SLEEP SPINDLES

As mentioned above, spindles are short-lasting (0.5–3 seconds), waxing and waning oscillations in the sigma range (11–16 Hz) during NREM sleep, especially during stage N2. Spindles are affected by a series of factors, including circadian modulation (Dijk & Czeisler, 1995a; Knoblauch, Krauchi, Renz, Wirz-Justice, & Cajochen, 2002; Knoblauch, Martens, Wirz-Justice, Krauchi, & Cajochen, 2003), age (Landolt, Dijk, Achermann, & Borbély, 1996), menstrual cycle (Driver, Dijk, Werth, Biedermann, & Borbély, 1996), and drugs (Aeschbach, Dijk, Trachsel, Brunner, & Borbély, 1994; Dijk et al., 1995). Behavioral and electrophysiological data further suggest a functional differentiation between

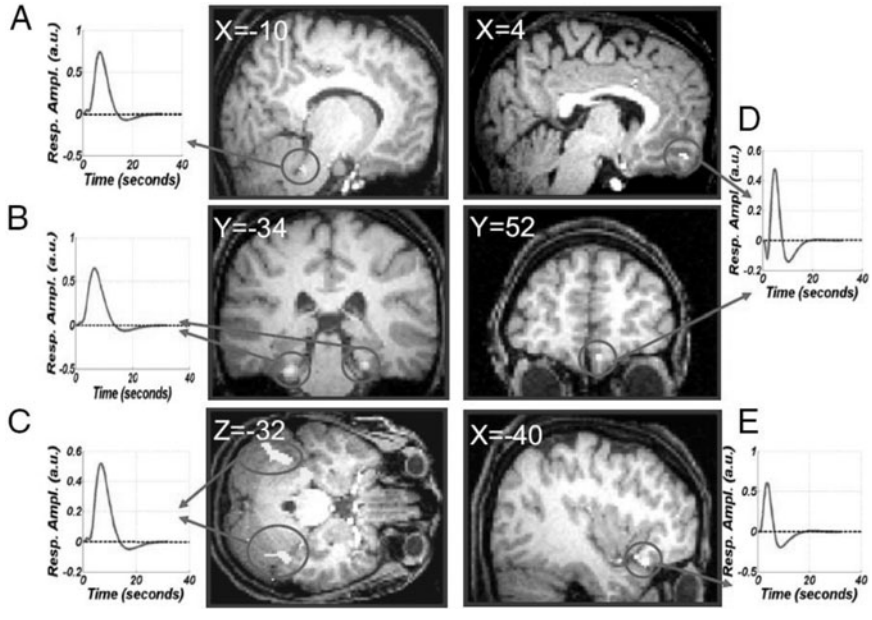


Fig. 1.9 Combined EEG-fMRI investigation of human NREM sleep. Panels show brain regions in which increased event-related BOLD responses are commonly associated with the depolarized (up) state of slow and delta waves. Associated curves show the time course of fitted response amplitudes (arbitrary units) during slow or delta waves in the corresponding circled brain area. (A) Pontine tegmentum. (B) Parahippocampal gyrus. (C) Cerebellum. (D) Medial prefrontal cortex. (E) Inferior frontal gyrus. (F) Posterior cingulate cortex. From Dang-Vu et al. (2008).

slow (11–13 Hz) and fast (14–16 Hz) spindles (e.g., for a review see De Gennaro & Ferrara, 2003), but their functional neuroanatomy remained uncertain. PET studies have yielded conflicting results, with a reported relationship between spindle activity and rCBF in the thalamus (Hofle et al., 1997) contradicted later on (Dang-Vu et al., 2005). Using a combined EEG-fMRI approach, Schabus and collaborators (2007) recently found that spindle occurrence is associated with transient increases in regional brain activity in thalamic and paralimbic areas (anterior cingulate and insular cortices) and the superior temporal gyrus (Figure 1.10). Besides a common neuroanatomical pattern, they also found that activity in distinctive thalamocortical networks characterizes fast and slow spindles. Whereas slow spindles elicit additional increased activity in only the frontal gyrus, fast spindles are associated with specific activations in a large set of cortical regions involved in sensorimotor processing, as well as in the orbital and mesial prefrontal cortex, hippocampus, and anterior insula, further supporting the hypothesis that generation of fast and slow spindles relies upon two functionally separated systems.

REM sleep

At variance with NREM, REM sleep and wakefulness are characterized by sustained, desynchronized neuronal activity (Steriade & McCarley, 1990) associated with high energy demands. Therefore, activity as measured using PET or fMRI will be increased in brain regions actively involved in REM sleep processes as compared to NREM sleep, even above activity levels observed during wakefulness. Using PET, REM sleep was associated with a specific neuroanatomical pattern of increased activity in the mesopontine tegmentum (PPT), thalamic nuclei, basal forebrain, cerebellum, caudate nucleus, limbic and paralimbic structures (e.g., amygdala, hippocampus, anterior cingulate cortex), and associative posterior temporo-occipital regions (Braun et al., 1997, 1998; Maquet et al., 1996; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997; Peigneux et al., 2001). In parallel, decreased regional CBF was found in frontal and parietal regions (dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus and inferior parietal cortex), as well as in primary sensory areas (Braun et al., 1997; Maquet et al., 1996, 2000, 2005), indicating that activity in these regions is strongly diminished during REM sleep (Figure 1.11).

Increased regional CBF activity in the PTT, thalamus, and basal forebrain is in line with the neurobiological literature, indicating that REM-on neurons and other cellular populations responsible for REM sleep induction are located in these regions and mediate widespread cortical activation through innervations in the thalamus and basal forebrain (Capece, Efange, & Lydic, 1997; Datta, 1995, 1997; Steriade & Buzsaki, 1990). Also, increased activity in amygdaloid complexes involved in the generation of REM sleep (Morrison, Sanford, & Ross, 1999) reflects their potential role in the modulation of

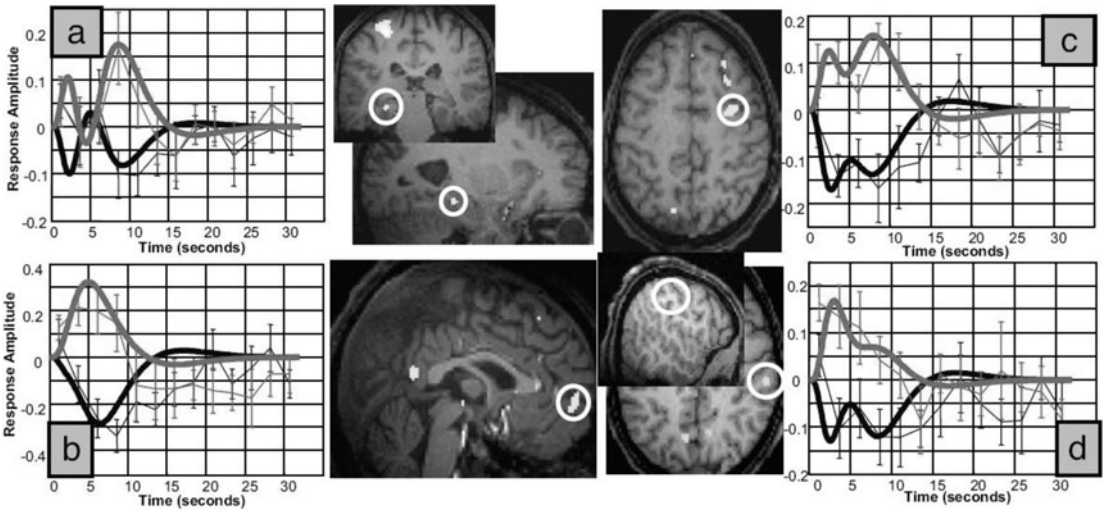


Fig. 1.10 Functional neuroanatomy of fast and slow spindles. Panels show larger brain responses for fast (red) than slow (black) spindles in the hippocampus (a), mesial prefrontal cortex (b), precentral gyrus (c), and postcentral gyrus (d). From Schabus et al. (2007).

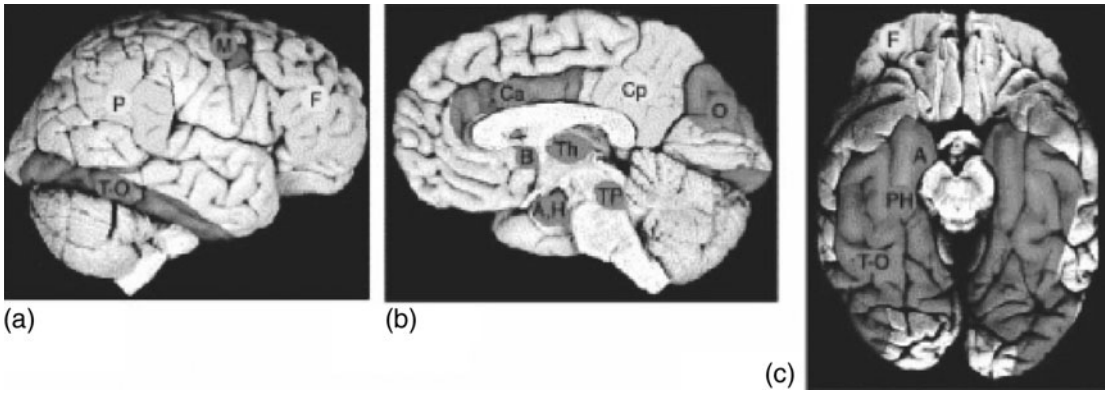


Fig. 1.11 Schematic representation of the functional neuroanatomy of normal human REM sleep (Braun et al., 1997; Maquet et al., 2000; Maquet et al., 1996; Nofzinger et al., 1997). Regions in red are those in which there is a relative increase in neural activity associated with REM sleep; regions in blue correspond to relative decreases in neural activity associated with REM sleep: (a) lateral view; (b) medial view; (c) ventral view. A: amygdala; B: basal forebrain; Ca: anterior cingulate gyrus; Cp: posterior cingulate gyrus and precuneus; F: prefrontal cortex (middle, inferior, and orbitofrontal cortices); H: hypothalamus; M: motor cortex; P: parietal cortex (inferior parietal lobule); PH: parahippocampal gyrus; O: occipital-lateral cortex; Th: thalamus; T-O: temporo-occipital extrastriate cortex; TP: pontine tegmentum. From Schwartz and Maquet (2002).

regional activation/deactivation patterns during REM sleep (Amaral & Price, 1984). Indeed, most activated areas during REM sleep are regions receiving numerous amygdalar projections, whereas deactivated frontal and parietal cortices are practically devoid of amygdalar afferents (Aggleton, 1993; Amaral, Price, Pitkänen, & Carmichael, 1992; Amaral & Price, 1984). Also, animal data have shown that electrical stimulation of the central nucleus of amygdaloid complexes increases phasic pontogeniculooccipital (PGO, see below) activity (Calvo, Badillo, Morales-Ramirez, & Palacios-Salas, 1987), one of the most distinguishing feature of REM sleep.

PHASIC AND TONIC ACTIVITIES IN REM SLEEP

Widespread thalamocortical synchronized activity characterizes both REM sleep and wakefulness, in line with PET results (Braun et al., 1997; Braun et al., 1998; Buchsbaum, Hazlett, Wu, & Bunney, 2001; Maquet et al., 1996; Nofzinger et al., 1997; Peigneux et al., 2001). Beyond regional patterns of sustained cerebral activity, however, fMRI investigations suggest that transient changes in thalamocortical activity reflect the transition between tonic and phasic components during REM sleep (Wehrle et al., 2007). Indeed, within human REM sleep, widespread activity in a thalamocortical network including limbic and parahippocampal areas seems to occur selectively during phasic REM sleep (e.g., rapid eye movement periods) as compared with the predominant tonic REM sleep background, suggesting that REM sleep subdivides into tonic REM sleep with residual alertness and phasic REM sleep with the brain acting as a functionally isolated and closed intrinsic loop. From an evolutionary point of view this transition may be beneficial, since phasic REM sleep constitutes an extremely vulnerable state during which sensory inputs are not perceived on top of decreased reactivity capacities due to general muscle atonia.

Probably the most distinguishing phasic feature of REM sleep are pontogeniculooccipital (PGO) waves, which are prominent phasic bioelectrical potentials occurring in isolation or in bursts during the transition from NREM to REM sleep or during REM sleep itself (for reviews, see Callaway, Lydic, Baghdoyan, & Hobson, 1987; Datta, 1999). In animals, REMs are closely related to the occurrence of PGO, which propagates throughout the brain but prominently in the pons, the lateral geniculate bodies and the occipital cortex. PGO are, however, a fundamental process of REM sleep, playing a significant role in central nervous system maturation (Datta & Patterson, 2003). In humans, intracerebral recordings in epileptic patients (Salzarulo, Lairy, Bancaud, & Munari, 1975) as well as noninvasive PET (Peigneux et al., 2001), fMRI (Wehrle et al., 2005), and magnetoencephalography (MEG; Ioannides et al., 2004) studies in healthy volunteers indicate that rapid eye movements observed during REM sleep are generated by mechanisms similar or identical to PGO waves in animals.

Conclusions

In this chapter, we have tried to guide the reader beyond the appearances of a cessation of waking activity during sleep. We have seen that despite evolutionary adaptations and divergences amongst species, sleep is a universal phenomenon whose generation and maintenance are under the control of complex regulatory mechanisms. Most importantly, we have learned that above all, sleep is a state of the brain, and even more a series of active states of the brain. Sleep-related changes in brain activity can be observed at neurobiological, neurophysiological, and neuroanatomical levels including, amongst others, cellular and molecular interactions, re-equilibration of the neurotransmitter balance, and changes in functional neuroanatomical patterns, eventually leading to REM and NREM sleep stages and their characteristic tonic and phasic patterns in humans. Our exponentially growing knowledge about the way sleep is regulated and organized at the brain level should ultimately allow answering the fundamental questions of the vital functions played by sleep in the life span.

Related chapters

The regulation of human sleep and wakefulness

Sleep homeostasis; circadian physiology; the two-process model; circadian, diurnal, and ultradian factors in sleep & wakefulness; sleep chronotypes; respiratory control; thermoregulation.

The functions of sleep

Evolutionary perspectives; body restitution; cerebral restitution; core and optional sleep; perspectives on REM sleep; sleep deprivation and its effects.

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CHAPTER 2

The Regulation of Human Sleep and Wakefulness

Sleep Homeostasis and Circadian Rhythmicity

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Abstract

The alternation of sleep and wakefulness is a major determinant of the structure and quality of our lives. The sleep–wake cycle is regulated by a fine-tuned balance between two physiological processes: sleep homeostasis, which measures sleep debt, and circadian rhythmicity, which determines the optimal internal (biological) time for sleep and wakefulness. Sleep homeostasis and circadian rhythmicity together influence many aspects of sleep, such as the time it takes to fall asleep, the timing of awakening and the interruptions of sleep, as well as the duration of rapid eye movement sleep, slow-wave sleep and specific brainwaves during sleep, such as sleep spindles. Alterations in the balance between sleep homeostasis and circadian rhythmicity contribute to sleep phenotypes such as morningness-eveningness and short-long sleepers as well as sleep disturbances. Emerging insights into the environmental, behavioral, physiological, neurochemical and molecular-genetic determinants of sleep homeostasis and circadian rhythmicity provide new avenues for the understanding and improvement of the sleep–wake cycle.

Keywords: sleep physiology, circadian rhythmicity, sleep homeostasis, slow-wave sleep, REM sleep, sleep spindles, sleep deprivation, individual differences, genes, polymorphisms, melatonin, light, photoreception, chronotypes

Assessment of sleep physiology

The regular alternation of sleep and wakefulness is a defining characteristic of our daily lives. We regain consciousness when we wake up in the morning, go about our work and social activities and then retire for sleep, during which we are unconscious for most of the time except for when we dream. Most of us will have no serious complaints about our sleep–wake cycle, except maybe that we don't get enough sleep, have the occasional bad night's sleep, or wish there were more hours in the day. We attribute functions to sleep when we blame the bad mood, lack of concentration or an embarrassing lapse of memory on insufficient sleep during the previous night, but probably do not subscribe to any comprehensive theory on sleep's contribution to brain function. Sleep physiologists have provided a detailed description of the changes in brain activity as well as changes in hormones and peripheral physiology during sleep. Sleep and circadian physiologists have uncovered some of the mechanisms underlying the alternation of sleep and wakefulness and provided clues about the functions of sleep—for the brain and the body. These insights on the mechanisms underlying normal sleep–wake regulation have also provided indications about the putative mechanisms underlying sleep disorders.

Within the context of the regulation of the sleep–wake cycle, nocturnal sleep is not viewed in isolation, but it is rather viewed within the context of circadian rhythmicity, i.e., all the rhythms that characterize human physiology and are synchronized to the rhythms in the environment. Nocturnal sleep is also viewed as part of the 24-hour day. It can be seen as a response to the duration and experiences of the previous wake period. Finally, nocturnal sleep can be viewed within the context of the subsequent wake episode. Nocturnal sleep may affect our behavior

the next day and the demands of the next waking period may also affect the quality and duration of our sleep. We will first provide an overview of the phenomenology of sleep and wakefulness.

The three vigilance states (Wakefulness, NREM, REM)

The physiology of sleep can be assessed by polysomnography, which is the simultaneous recording of many physiological variables. Recordings of the patterns of electrical activity of the brain by placing electrodes at the surface of the scalp (electroencephalogram, or EEG), recordings of the tone of muscles (electromyogram, or EMG), recordings of the movements of the eyes (electrooculogram, EOG), respiration and the electrocardiogram (ECG) reveal the changes that take place in the brain and body when we transition from wakefulness to sleep. During wakefulness, the eyes are open and show fast saccadic movements while tracking objects. When we lie down and close our eyes, these rapid eye movements give way to slow rolling eye movements indicating the lack of focus on objects in the visual field. At the same time, the tone of skeletal muscles drops and high-frequency, low-amplitude EEG oscillations give way to EEG oscillations that are characteristic for drowsiness and sleep. Beta waves (20–40 Hz oscillations) subside and alpha waves (8–12 Hz oscillations) appear. These then give way to theta waves (4.5–8 Hz); K-complexes, which are isolated sharp negative EEG deflections; sleep spindles (12–15 Hz 0.5–2 second long spindle trains) and slow waves 0–4 Hz, large amplitude oscillations also called slow wave activity, SWA (See Figure 2.1). The EEG becomes more and more dominated by slow waves and throughout these periods of sleep the eyes are not moving. This phase of sleep is referred to as non-rapid eye movement sleep or slow-wave sleep. In adults, depending on their age (Ohayon et al., 2004), after an average of 60–90 minutes, the EEG reverts abruptly to a pattern similar to the transition stage between wakefulness and sleep. Low-amplitude theta-like waves with the occasional alpha train now make up the EEG trace. Muscle tone remains, but very low—virtually absent. The eyes now display rapid eye movements and this is why this sleep stage is referred to as rapid eye movement. It is also referred to as paradoxical sleep to indicate that while the EEG patterns appear activated, the individual is asleep. Characterization of NREM, REM and wakefulness by the analysis of numerous physiological variables and their interrelations indicate that these are truly different states and they are sometimes referred to as the three vigilance states or the three states of being. Coma and anesthesia are also considered states that are different from the normal physiological states and will not be considered here. Understanding the alternation between wakefulness, NREM, and REM sleep, and their regulation in response to changes in the time allowed for any of them—i.e., sleep deprivation and extension, as well as the interaction with endogenous circadian rhythmicity, clocks that continue to tick even in the absence of external time cues or behavioral cycles—has been the aim of many scientific investigations. In these investigations, sleep is quantified in a standard manner which we will describe next.

Characteristics of sleep in good sleepers

The progression in the changes of the EEG and sleep stages in the course of a sleep episode can be quantified by visual inspection of consecutive 30-second epochs of these polysomnographic traces, or by computer-assisted signal analyses such as the Fast Fourier Transform or other methods (see Figure 2.2). A graph of sleep stages, slow waves, and sleep spindles against time reveals the dynamic character of sleep (see Figure 2.3). After the lights are turned off, it takes the good sleeper on average 10–15 minutes to reach stage 1, and several more minutes to reach stage 2 (Carskadon & Dement, 1996; Ohayon et al., 2004). When asked in the morning how long it took to fall asleep, good sleepers will report an average of 15–30 minutes, suggesting that the onset of stage 2 is related to the subjective onset of sleep, although wide discrepancies between objective and subjective measures of sleep latency have also been reported in good sleepers (Baker et al., 1999; Majer et al., 2007).

After the first episode dominated by slow waves, referred to as SWS or N3, REM sleep occurs. The interval between sleep onset (usually defined as the first occurrence of stage 1 or 2) and REM sleep is referred to as latency to REM sleep and in healthy young sleepers averages 70–100 minutes. The first REM episode is generally short. Together, the first NREM and first REM episode constitute the first NREM–REM cycle. A prototypical 8-hour sleep episode contains four or five of these NREM–REM cycles. Whereas the duration of the entire cycle doesn't change much in the course of a sleep episode, the duration of NREM and REM episodes does. At the beginning of a nocturnal sleep episode the REM episodes are short and the NREM episodes are long. In the course of a nocturnal sleep episode REM episodes become longer a NREM episodes become shorter (Feinberg & Floyd, 1979).

According to the scoring criteria for human sleep, a good sleeper will return to wakefulness, i.e., at least one 30-second polisomnography (PSG) epoch scored as W, as often as 15–20 times per night. Many of these awakenings will occur at the transitions between NREM and REM sleep and in association with adjustments of body position. These awakenings last only 30–60 seconds or so and will not be remembered in the morning. In fact, good sleepers, when asked in the morning, will report an average of only 1–3 awakenings.

Quantification of the time course of slow waves and sleep spindle activity reveals more of the dynamic characteristics of sleep. Whereas in the first NREM episode SWA activity rises fast and high levels of SWA are observed, the rise rate of SWA and maximum levels attained within a NREM episode decline gradually as the night progresses. It should be noted that even though the latter part of sleep consist primarily of stage 2 and REM sleep, this stage will still contain some slow waves.

In contrast to SWA, the maximum values of sleep spindle activity do not change much in the course of sleep, except for a minor increase toward the end of the sleep episode. Within each NREM episode, neither SWA nor sleep spindle activity is constant, but instead display a typical dynamic. SWA rises gradually to reach its highest levels in the middle and last part of the episode before it drops suddenly just prior to the onset of REM sleep. In contrast, the time course of sleep spindle activity resembles a U-shaped pattern with high levels at the beginning and end of each NREM episode (Dijk et al., 1993). Analyses of the dynamics of slow waves and sleep spindles based on the simultaneous recording of hundreds of electrodes revealed that slow waves are dominant in frontal derivations, and to a large extent originate in frontal areas and behave as a travelling wave with other (temporal and parietal) cortical areas as their destination (Massimini et al., 2004). Sleep spindles are most prominent along the midline derivations and differ in their frequency between frontal and more posterior derivations (De Gennaro & Ferrara, 2003). Thus, slow waves and sleep spindles display dynamics within and across NREM episodes, and these dynamics also exhibit topographical specificity.

SLOW WAVES, SLEEP SPINDLES, AND EEG ACTIVATION

Because the EEG plays such an important role in scoring the vigilance states and changes in the EEG have been central in describing sleep regulatory processes, a brief description of the underlying mechanisms is provided. The EEG patterns as derived from a single scalp electrode reflect the behavior of thousands of cortical neurons. Intracranial recording in animals and in a few studies in human subjects, usually epileptic patients, have demonstrated that the firing patterns of cortical neurons change from a single spike tonic firing mode to a burst-pause pattern at the transition from wakefulness to NREM sleep. In the latter mode, single neurons display the slow oscillation, in which a phase of hyperpolarization of the membrane potential is followed by a depolarization and a burst of action potentials. These phenomena are associated with the flow of currents in and out of the dendrites, axons and soma of neurons and these current flows lead to changes in the local field potential. The synchronization of the slow oscillation (~1Hz) in thousands of neurons leads to the appearance of slow waves in the surface EEG. The occurrence of slow oscillations and their synchronization depends on both the dissipation of activating inputs from noradrenergic, serotonergic, histaminergic and cholinergic modulatory systems, as well as the local connectivity in cortical networks. Sleep spindles are observed in the cortex and in the thalamus and are strongly dependent on the nucleus reticularis of the thalamus (Crunelli & Hughes, 2009; Esser et al., 2007; Steriade, 2003).

Body, skin and brain temperature during sleep

Sleep is associated with changes not only in the EEG but also in many other physiological variables, which may contribute to the sleep process and our experience of it. Core body temperature drops at the onset of sleep and reaches its lowest levels in the last part of the nocturnal sleep episode. This drop in core body temperature reflects the combined influences of sleep and associated changes in activity and body posture, as well as the influence of endogenous circadian rhythmicity. In the absence of sleep and under constant routine conditions, i.e., when a volunteer is kept awake in a constant posture and in dim light, core body temperature will continue to oscillate and reach its circadian nadir approximately 1–3 hours before habitual wake time and reach its crest 2–4 hours before habitual bedtime. In the presence of sleep, the amplitude of the rhythm in core body temperature is much greater. One important contributor to the drop in temperature during sleep is the change from the upright to the supine posture, which normally precedes sleep onset.

A drop in core body temperature is to a large extent a consequence of the dissipation of body heat. This dissipation of body heat is associated with a rise in skin temperature, in particular in the extremities. Highest skin temperatures are observed at sleep onset due to vasodilatation in the hands and feet. This heat loss is closely associated with the time it takes to fall asleep, suggesting that temperature regulation and sleep initiation are closely interrelated (Krauchi, 2007). For the remainder of the sleep episode, the associations between temperature and sleep are unremarkable. In humans, core body temperature and skin temperature are not substantially modulated by the NREM–REM cycle, even though animal studies have clearly documented brain temperature to be affected by the NREM–REM cycle.

Respiration, heart rate and blood pressure during sleep

In healthy sleepers, respiratory rhythms continue uninterrupted during sleep in an autonomous way. Respiratory rates in general drop during NREM sleep and respiration can become irregular and shallow during REM sleep. Challenge studies have indicated a reduced responsiveness to CO2 and the reduced muscle tone during sleep and REM sleep in particular may contribute to the occasional collapse of the upper airway and cessation of airflow in the presences of respiratory effort (Krimsky & Leiter, 2005).

Heart rate drops at sleep onset, and heart rate is modulated considerably by the NREM–REM cycle. Heart rate reaches its lowest levels during NREM sleep and this is in part due to a shift in the sympathovagal balance, from sympathetic to parasympathetic dominance. During REM sleep, heart rate increases and analyses of its variability indicate a much stronger sympathetic input to the heart (Jurysta et al., 2003). In healthy sleepers, blood pressure drops during sleep at night and studies in which subjects are kept awake at night indicate that these nocturnal changes in heart rate and blood pressure as well as respiration, are to a large extent sleep-dependent, i.e., the amplitude of the nocturnal changes in the absence of sleep is only minimal.

Hormone release during sleep

When sleep occurs at night, it occurs in a particular endocrine environment. The plasma concentrations of melatonin, the hormone secreted by the pineal gland, will have started to rise 1–2 hours before habitual bedtime. It will maintain high levels throughout the nocturnal sleep episode, but during the waking day levels are very low. The rhythm of melatonin will persist in the absence of sleep provided light levels are modest and we now know that its rhythm is driven by the suprachiasmatic nucleus, locus of the circadian pacemaker in humans and other mammals through a well-characterized polysynaptic pathway. When we go to sleep at night, plasma concentrations of the hormone cortisol, synthesized and secreted by the adrenal cortex, are very low, and they will continue to rise throughout the sleep episode, to reach their daily peak levels, at around habitual wake time. The rhythm of this hormone is also nearly sleep-independent, i.e., it persists in the absence of sleep. Sleep only slightly inhibits cortisol. It is a connection from the circadian clock which resides in the Suprachiasmatic Nucleus (SCN) of the hypothalamus, to the paraventricular nucleus of the hypothalamus that drives the release of the cortisol releasing factor, which in turn drives ACTH release from the anterior pituitary in the general circulation, which then drives cortisol synthesis from the adrenal cortex.

At sleep onset and during SWS in particular, the anterior pituitary will release a surge of growth hormone. In the absence of sleep, no nocturnal surge of growth hormone is observed and the release of this hormone is very much sleep-dependent. Other hormones in which the release is sleep- or rest-dependent include prolactin and thyroid-stimulating hormone as well as the appetite-regulating hormones ghrelin and leptin (Czeisler & Klerman, 1999; Spiegel et al., 2004).

Assessment of wakefulness

Sleep and wake propensity

Analysis of sleep within a 24-hour context requires that we quantify both sleep and wakefulness. Within the context of sleep regulation, wakefulness is mostly viewed as the absence of sleep, the absence of sleepiness and the ability to perform behaviors typical for wakefulness. Subjective assessment of sleepiness while people are conducting their daily activities reveals that immediately upon awakening we are still somewhat sleepy, that this sleepiness/fatigue then dissipates to a minimum later in the morning and early afternoon, and then increases again (Kahneman et al., 2004).

Assessment of the ability to fall asleep in the laboratory as measured by polysomnography in the Multiple Sleep Latency Test (MSLT) yielded patterns of sleep propensity, in which the longest latency to sleep is present when first assessed approximately 2 hours after habitual sleep onset. This is

followed by a reduction in sleep latency to reach a minimum at approximately 2–4 p.m., and hereafter sleep latencies increase again (Carskadon & Dement, 1982). The time course of theta activity in the waking EEG, which is often considered an electrophysiological marker of sleepiness, increases during the day. This increase continues during sleep deprivation, albeit modulated by a circadian phase so that in the evening hours levels are somewhat lower (Finelli et al., 2000). Thus the diurnal patterns of both subjective sleepiness/fatigue or objective sleepiness do not reflect a simple progressive increase with time awake but instead show non-monotonic and somewhat counterintuitive patterns. Variation in MSLT values within and between individuals have been reported. Several studies show that within a narrow age cohort of a healthy good sleeper, short habitual nocturnal sleep duration is associated with increased daytime sleepiness, i.e., shorter MSLT values and higher subjective sleepiness and extension of sleep leads to a reduction of daytime sleepiness (Arand et al., 2005; Kamdar et al., 2004).

Performance

When sleep is viewed as a recovery process maintaining the integrity of brain function, the assessment of our ability to perform during wakefulness becomes relevant for sleep research and the evaluation of sleep quality. Assessment of the diurnal patterns of performance on a variety of tasks demonstrates that immediately upon awakening, performance is impaired, and this phenomenon is referred to as sleep inertia (Scheer et al., 2008). Performance then recovers and remains fairly constant over most of the waking day. Minor variations in performance are observed and these variations depend on factors such as workload, task difficulty, etc. The often mentioned mid-afternoon increase in sleep propensity is in general not accompanied by a major decline in performance. Thus a healthy individual can uphold performance throughout a normal waking day. Sleep restriction will, however, lead to an impairment of waking performance (Banks & Dinges, 2007). A stable level of performance during the day and lack of sleepiness are indicators of sufficient sleep.

Sleep homeostasis

The description of the phenomenology of the sleep–wake cycle in good sleepers begs the question of which factors underlie its regulation and how various aspects of its phenomenology interrelate. Do we go to sleep because we have been awake for 14–17 hours and do we wake up because we have slept enough, or is the sleep–wake cycle governed by a simple clock that keeps track of only time and not of sleep need? If we use an alarm clock, does this imply that we override our internal sleep-timing mechanisms and have not had enough sleep?

As described, the phenomenology of a nocturnal sleep episode is complex: After the lights are turned off, sleep onset occurs after 10–15 minutes SWS is high at the beginning of the nocturnal sleep episode, REM sleep is abundant at the end of the nocturnal sleep episode and then we wake up. What underlies this phenomenology? Is it determined by time-of-day/clock-like influences on sleep propensity and structure, or do sleep propensity and the changes in sleep physiology simply reflect a response to the duration and characteristics of the previous wake episode and the progression of the sleep process? To answer these questions, sleep scientists have manipulated the sleep–wake cycles of good sleepers in many different ways and sleep deprivation has been among the most popular approaches. This approach is inspired by the concept of homeostasis, which in the context of sleep regulation, implies that sleep occurs when certain variables/parameters deviate from a set point or reference level and that sleep restores these variables/parameters to this reference level (see Figure 2.4). The deviations are, in general thought to be a consequence of the duration of wakefulness, but specific conditions such as infections, etc., could also lead to a greater sleep need.

Total sleep deprivation

Staying awake for one night and the next day and then going to sleep at a habitual bedtime represents one night of total sleep deprivation. In a young adult it entails losing 8 hours of sleep—2 hours of REM sleep, 2 hours of SWS and another 4 hours of stages 2 and 1 sleep. At the same time, wakefulness preceding sleep increases from 16 hours to 40 hours or so. What are the characteristics of recovery sleep from total sleep deprivation? Not all of the lost sleep is immediately recouped and recovery sleep is indeed not 16 hours in duration. Unfortunately, in most studies the time allowed for a recovery sleep episode was restricted. Therefore not much information on the duration of recovery sleep after total sleep deprivation under unlimited sleep opportunity conditions is available. In one such study in which subjects were in bed for 24 hours, subjects slept approximately 5 hours more after one night of sleep deprivation compared to no sleep deprivation (Rosenthal et al., 1991). When we consider the

sleep deprivation studies in which recovery sleep was restricted, we will find that the two hours of lost REM sleep are not regained. In fact, in young adults, REM sleep during recovery sleep from total sleep deprivation may be somewhat below baseline. The rhythmicity of the NREM–REM cycle is also not much affected, illustrating its ultradian clock-like regulation, which is unperturbed by total sleep loss. The lost time in stages 2 and 1 sleep is not recovered, but indeed less time is spent in these stages than at baseline. The main differences between recovery sleep and baseline sleep are the reduced latency to sleep onset, the reduced number of awakenings and the increased contribution of SWS/SWA (Borbély et al., 1981). These findings have been interpreted as evidence for the predominance and importance of SWS. Quantitative analyses of the EEG and its dynamics have shown that after sleep deprivation the transition of spindle-dominated to slow-wave-dominated EEG occurs at a more rapid rate. These analyses have also revealed that the increase in SWA is short lived. At the end of an 8-hour recovery sleep episode, SWA is indistinguishable from baseline. A more detailed picture of the dynamics of recovery sleep can be obtained by initiating recovery sleep after 36 hours of wakefulness, i.e., 4 hours before habitual bed time. If subjects are also instructed to stay in bed until at least noon the next morning, Total Sleep Time (TST) on average will be 13.5 hours. An increase of SWS and SWA above baseline is observed, but also under these conditions the increase in SWS/SWA is short lived (Dijk et al., 1990).

In summary, total sleep deprivation leads to an increased sleep propensity, sleep consolidation, and enhanced SWS/SWA, but not all lost sleep is or can be recovered immediately.

Total sleep deprivation experiments also allow for an assessment of the time course of performance and sleepiness during the day–night cycle. Sleepiness increases and performance deteriorates when subjects enter the first night without sleep, and a first nadir in performance is observed at approximately 6–9 a.m., the exact timing depending on the nature of the task. Hereafter, performance improves somewhat during the next day but remains below baseline, indicating that one night of lost sleep will have a negative impact on waking performance the next day (Cajochen et al., 1999). In a few experiments in which sleep deprivation was extended to 64 hours or more, the time course of performance clearly indicates that it is determined by both a time of day component, with a nadir in performance late in the biological night, and a component related to the progressive deprivation of sleep (Lim & Dinges, 2008). Although recovery of performance after sleep loss hasn't been studied in great detail, the available data show that some aspects of performance when assessed during the daytime recover almost immediately after one recovery sleep period, although other aspects may take more time to recover (Belenky et al., 2003).

Partial sleep deprivation

Partial sleep deprivation, in which sleep is restricted to 6, 4, or fewer hours of sleep, is probably a more ecologically valid model of sleep deprivation, or at least one to which we can more easily relate. In principal, partial sleep deprivation can be achieved by either postponing sleep onset, advancing sleep end, or a combination of the two. As far as its effects on the type of sleep lost are concerned, the results are equivocal. This is because SWS will always dominate the beginning of sleep, and partial sleep restriction therefore leads primarily to a reduction in stage 2 and stage 1 as well as REM sleep. Partial sleep deprivation will lead to an increase in sleep propensity as measured by sleep onset latencies at the beginning of the nocturnal sleep episode and a reduced number of nocturnal awakenings. It will also lead to an enhancement of SWS, even though very little SWS, but some SWA is lost. The dynamics of the response to a partial-sleep-deprivation regime has been described in studies in which the regime is maintained for 4 to 7 days or so (Akerstedt et al., 2009; Brunner et al., 1993). The increase of SWA levels off at approximately 120% after only a few days, sleep efficiency is as high as 96% and REM sleep will constitute nearly 30% of TST. Alpha/Theta activity in REM sleep progressively declines. The effects of chronic partial sleep deprivation are not restricted to sleep. Daytime sleep propensity as assessed by the MSLT increases in the course of a sleep restriction period (Carskadon & Dement, 1981). Waking performance is also affected in a negative way. For example, lapses on a psychomotor vigilance task will increase dramatically. Unlike the increase in SWA and subjective sleepiness, which level off after a few days, performance continues to deteriorate progressively in the course of the chronic partial sleep restriction (Dinges et al., 1997). Performance during the daytime, however, appears to recover swiftly after one or two nights of 8–10 hours of sleep.

Selective sleep deprivation

The question whether deprivation of either SWS or REM sleep leads to a differential effect on sleep and

waking performance has been addressed in selective sleep deprivation experiments. Stimuli delivered when slow waves appear in the EEG can prevent the subject from entering deep SWS (Agnew et al., 1967). Hundreds of very loud acoustic stimuli (up to 100dB) are required for successful SWS deprivation, which will lead to arousals but will hardly affect TST, REM sleep or the NREM–REM cycle and primarily replaces SWS by stage 2 and stage 1 sleep. If the SWS deprivation is terminated after a few hours, an intra-night rebound of SWS/SWA will occur. Thus the decline in SWS/SWA normally observed in a sleep episode appears to be dependent not only on the time asleep but also of how much SWS/SWA was obtained (Dijk et al., 1987b). If the SWS/SWA deprivation is continued throughout the sleep episode, and no daytime naps are allowed, SWS will be enhanced in the next undisturbed sleep episode (Ferrara et al., 1999). Thus the SWS deficit incurred during the SWS deprivation is carried over the intervening wake episode to be expressed in the next recovery sleep episode. Consequences of SWS deprivation for daytime functioning have also been studied. They include increases in daytime sleep propensity and some decrements in performance, although the question of whether these effects are specific to SWS lost or are related to the increased number of arousals has not been answered definitely (Bonnet, 1986; Walsh et al., 1994). SWS deprivation also has consequences for metabolic function and glucose regulation (Tasali et al., 2008). Two recent studies indicate that SWS deprivation may affect consolidation of perceptual learning and visuomotor learning (Aeschbach et al., 2008; Landsness et al., 2009).

Selective deprivation of REM sleep cannot be accomplished without awakenings, unless pharmacological tools are used. As soon as the first signs of REM sleep appear in the polysomnogram, the subject is awakened (Agnew et al., 1967). After a few minutes, return to sleep is allowed, but this will nearly always be a return to NREM sleep. By repeating this procedure whenever signs of REM sleep appear, REM sleep can be almost completely abolished without major changes in total sleep time or SWS, although some changes in sleep structure occur. In the course of one night or several nights of REM sleep deprivation, more and more awakenings are required, which has been taken as evidence for the accumulation of a REM sleep deficit. Indeed, recovery sleep after several nights of REM sleep deprivation is characterized by an increase in REM sleep, demonstrating also that REM sleep is to some extent under homeostatic control (Endo et al., 1998). This homeostatic control can already be observed within one night of REM sleep deprivation (Beersma et al., 1990).

Extra sleep: Naps and sleep extension

The manipulation opposite to restriction/deprivation is extension of the sleep opportunity, and these extension studies have also provided insight into the homeostatic regulation of sleep. Scheduling naps either in the morning or in the afternoon/early evening, extending the nocturnal sleep episode by a few hours, or scheduling people to be in bed in darkness for up to 16 hours per 24 hours for several days are among the approaches used.

Nap studies have demonstrated that most young adults can initiate sleep during the day and that the sleep structure of the naps varies in a predictable way. Early morning naps contain little SWS and consist primarily of stage 2 and REM sleep. Afternoon and evening naps contain more SWS and less REM sleep (Dijk et al., 1987a; Karacan et al., 1970). These changes in sleep structure are particularly clear when only one nap per day is taken and a nap in the afternoon is thereby preceded by a longer wake period than a morning nap. In fact, both SWS and SWA in the initial part of naps increase monotonically with the duration of wakefulness (Dijk et al., 1987a). The influence of naps on subsequent nocturnal sleep has also been studied. Whereas early morning naps were shown to have little effect on subsequent nocturnal sleep, naps in the afternoon or early evening lead to profound effects. In one study it was reported that following an early evening nap SWS was reduced from 81 to 52 minutes and EEG-assessed sleep latency increased from less than 10 to more than 35 minutes. Subjective sleep latency increased from less than 15 minutes to more than 45 minutes (Werth et al., 1996) (See Figure 2.5). An evening nap can turn a good sleeper into a sleeper with sleep onset problems! The differential effects of morning and afternoon sleep can be understood based on the very different sleep structure contents of these naps and can also be understood within the context of the two-process model of sleep regulation and the time course of the sleep homeostatic process.

Early studies indicated that extending sleep for one night has only minor effects on the subsequent nocturnal sleep structure. Fundamental questions about sleep regulation can be addressed by extending sleep opportunities to 10, 14, or 16 hours or so for many nights (Klerman & Dijk, 2008; Klerman & Dijk,

2005; Roehrs et al., 1996; Wehr, 1991). These studies have shown that TST is initially well above our habitual sleep time by as much as 4 or 5 hours. After a few days on this extended sleep opportunity schedule, this increase in total sleep time becomes smaller, although in general it remains above baseline. For young adult good sleepers, estimation of the asymptotic sleep durations, i.e., the maximal capacity for sleep when given ample opportunity for many days, averages approximately 8.9 hours, with an average of 2 hours of REM sleep (Klerman & Dijk, 2008). Please note that whereas TST remains above baselines, sleep efficiency, which is total sleep time divided by the duration of the sleep opportunity, will fall well below baseline. Thus sleep, although longer, becomes also less consolidated. At the same time, daytime sleepiness and performance are improved (Kamdar et al., 2004; Roehrs et al., 1996).

Models and physiology of sleep homeostasis

TIME COURSE/TIME CONSTANTS OF HOMEOSTASIS

The data summarized above provide strong evidence that sleep is not just an optional behavior but rather a state regulated in response to the sleep–wake history. Sleep loss leads to changes in daytime sleepiness and decrements in performance. Sleep loss and sleep extension also lead to changes in the consolidation and structure of subsequent sleep. The regulation of the various aspects of sleep varies with respect to the precision and the time course of the compensatory responses. Total sleep time and REM sleep duration respond slowly to deficits and clear dose-response relations have not always been obtained. In contrast, deficits in SWS/SWA are almost immediately recovered and in a very precise way. Quantitative models on the homeostatic regulation of sleep and its underlying neurochemistry are almost entirely based on the regulation of SWS/SWA. Both human and animal data show that SWA behaves like an hourglass oscillator (Borbély & Achermann, 1999). The propensity for SWA increases in a saturating exponential way during wakefulness and, when averaged per NREM episode, declines exponentially during sleep (Dijk et al., 1987a; Dijk et al., 1990). More detailed models, which incorporate the NREM–REM cycle, allow for a description of the dynamics of SWA across a nocturnal sleep episode in great detail (Achermann et al., 1993). More recent models allow for a description of the changes in NREM EEG power spectra in the course of a sleep episode (Esser et al., 2007). The essential assumptions of these recent models (Krueger et al., 2008; Tononi & Cirelli, 2006) are that during wakefulness, changes in connectivity of cortical networks or neurochemical changes occur, which ultimately lead to the initiation of SWS, during which these changes are reversed. The accurate regulation of SWS should not be taken as evidence that total sleep time is not an important determinant of the recovery aspect of sleep. In fact, the chronic partial sleep deprivation experiments during which very little SWS is lost, but a substantial part of total sleep time is lost, lead to significant performance decrements. Nevertheless, the precise regulation of SWS has inspired much research into the underlying mechanisms.

USE-DEPENDENT CHANGES IN NEURAL NETWORKS AND SWS HOMEOSTASIS

During wakefulness, cortical neurons fire in the typical phasic single action potential mode, while we are engaged in multiple behaviors and diverse experiences. These activity patterns and experiences are thought to lead to increases in synaptic strength of neural networks. These changes in synaptic strength are similar to those involved in long-term potentiation and reflect plasticity of the brain in response to experiences during wakefulness. This increased connectivity will lead to an increased likelihood of synchronized oscillatory behavior, which during sleep is expressed as SWS/SWA. Evidence for this scenario includes the observation that sleep regulation in humans also displays local aspects. Networks in most brain areas will be used extensively, and in the course of the waking day, overall synaptic strength will increase. Some areas, however, may be used more extensively than others and indeed local activation of, for example, the left somatosensory cortex through vibration of the right hand for 6 hours prior to sleep will lead to slightly more SWA in this particular brain region (Kattler et al., 1994). Likewise, constraining an arm during wakefulness will lead to a reduction in SWA (Huber et al., 2006). During SWA the strength of the synapses is downscaled, and this downscaling is necessary because of space and energy limitations (Tononi & Cirelli, 2006). This scenario provides a link between the concept of sleep homeostasis and changes in neural networks, plasticity and even memory consolidation.

ADENOSINE AND OTHER NEUROCHEMICAL CORRELATES OF SLEEP HOMEOSTASIS

The neural activity patterns during wakefulness are also accompanied by neurotransmitter release and high levels of energy metabolism to sustain firing rates and the required repolarization of membrane

potentials. The associated neurochemical processes could provide a basis for SWS homeostasis. The neurochemical that has received the most attention is adenosine, which is a by-product of energy metabolism. It is assumed that the wake-dependent increase in adenosine concentrations, through its effects on adenosine receptors, leads to either activation of sleep active neurons in the ventrolateral preoptic area, changes in neuronal potassium currents, or global cortical disfacilitation (Landolt, 2008). The direct relevance for sleep–wake regulation in humans relates to the effects of caffeine. Caffeine acts as an antagonist at adenosine receptors and by blocking the effects of adenosine can counter the sleep deprivation-associated decrements in performance, even during wake periods that are as long as 28 hours (Wyatt et al., 2004). Genetically determined differences in adenosine deaminase as well as polymorphism in the gene coding for the adenosine receptor have been shown to predict differences in SWS. Many other neurochemical changes may contribute to SWS homeostasis and individual differences therein (Krueger et al., 2008). They may include cytokines as well as classical neurotransmitter systems such as dopamine and serotonin.

Circadian rhythmicity

Many behaviors and physiological variables continue to oscillate within a near 24-hour period when animals are kept under constant environmental conditions. This includes the rest–activity and sleep–wake cycles. Thus, when kept in constant darkness for many months, the activity pattern of a rat or mouse will display an alternation of an episode of high levels of activity with an episode of low levels of activity, and the total duration of these two periods is approximately 24 hours. A perturbation of the rest–activity cycle by for example a 6- or 12-hour sleep deprivation does not abolish this rhythm and does not lead to a 6- to 12-hour shift of the rhythm. Similar observations have also been made in diurnal species, including squirrel monkeys and humans and this has led to the recognition that self-sustained biological oscillators, the molecular mechanisms that have been described in some detail, govern the timing of behavior. In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus is the locus of the circadian pacemaker, imposing rhythmicity on the rest of the brain and the body (see Figure 2.6). From a sleep regulation perspective, we consider the circadian clock to be self-sustaining not only because it does not require rhythmic input from the environment but also because it continues to oscillate in the absence of sleep–wake behavior. Does this imply that we go to sleep and wake up in the morning because our biological clock tells us to do so? To investigate this question, sleep scientists have studied humans under conditions very similar to those the animals were subjected to by circadian biologists, i.e., free-running conditions. Human circadian biologists have also used protocols to assess the extent to which the sleep–wake cycle leads to rhythmic variation in other variables and the extent to which circadian rhythmicity in these variables persists in the absence of a sleep–wake cycle.

Evidence for endogenous circadian rhythmicity in humans from free-running studies

Early approaches to the study of the circadian regulation of sleep in humans involved underground windowless bunkers, caves and hospital basements in which volunteers were studied for many weeks or months while in social isolation (for review see Czeisler and Dijk, 2001). The volunteers had no access to time-of-day information, and the light–dark cycle was under the control of the subjects and thereby was also devoid of time-of-day information. From these experiments, several key characteristics of human circadian rhythmicity emerged. Most importantly, the sleep–wake cycle persists with a period that varies from 24 hours and the ratio of wakefulness to sleep remains close to 2:1. Thus even though the synchrony with the 24-hour cycle is lost, the internal organization persists. Several changes in the internal organization do, however, occur. Whereas under normal conditions sleep is initiated approximately 6 hours before the nadir of the core body temperature rhythm, under free-running conditions the body temperature nadir is located very close to the beginning of sleep and sleep termination occurs 6–8 hours after the temperature nadir. This delay of sleep initiation relative to the temperature rhythm is also associated with a change in the intra-sleep episode dynamics of REM sleep. Whereas under entrained conditions, the first REM episode is very short. It is much longer under free-running conditions. At the same time, the dynamics of SWS are not greatly affected. After several weeks under these free-running conditions, many individuals display a phenomenon called spontaneous desynchrony, during which the periodicity of the sleep–wake cycle is very different from the stable near-24-hour periodicity from the core body temperature rhythm. Near-24-hour sleep–wake cycles alternate with sleep–wake cycles as long as 40–50 hours. Analyses of the

interaction between the sleep–wake oscillator and temperature oscillator have revealed a number of regularities (Czeisler et al., 1980a; Zulley et al., 1981). When sleep is initiated on the rising limb of the core body temperature rhythm, its duration can be as short as 5 hours, whereas sleep episodes initiated a few hours before the crest of the core body temperature rhythm can be very long, up to 18 hours or so. Considering the duration of the wake episode preceding these sleep episodes did not reveal a major contribution of "sleep homeostasis" (Strogatz et al., 1986). Interestingly, polysomnographic recording of sleep has demonstrated that SWS declined in the course of the sleep episode, whether it occurred on the rising or falling limb of the core body temperature rhythm (Weitzman et al., 1980). In contrast, REM sleep was linked to the core body temperature rhythm. These data were interpreted as evidence for the regulation of the sleep–wake cycle by two oscillators, a deep stabile circadian oscillator driving the core body temperature rhythm, and a labile sleep–wake oscillator linked to SWS. Forty years after the first description of this phenomenon of spontaneous internal desynchronization, the brain basis of it remains unknown. The recognition that besides the suprachiasmatic nucleus multiple circadian oscillators exist in various brain structures in other mammals as well makes the phenomenon less exotic or specifically human, although not better understood. Research subsequent to the discovery of human circadian rhythmicity internal desynchrony has focused on understanding the characteristics of the deep circadian oscillator, entrainment of the oscillator to the 24-hour day and the interaction between the sleep–wake oscillator and the deep circadian oscillator (Czeisler & Gooley, 2007). The sleep–wake oscillator is often considered synonymous to the hourglass process underlying SWS/SWA regulation and the deep oscillator is thought to be identical to the circadian oscillator located in the suprachiasmatic oscillator. Although definite evidence for either assertion is currently lacking, much progress in the understanding of human sleep–wake regulation has been made by quantifying the parameters of these two separate processes.

Evidence for endogenous circadian rhythmicity from constant routine protocols

Another approach to assess endogenous circadian rhythmicity is to observe multiple physiological and behavioral variables in subjects who are kept awake for 40 hours or so under constant conditions. In this context, constant conditions imply constant dim light, a constant posture and a constant vigilance state, i.e., wakefulness. Events such as large meals, which may induce apparent rhythmicity in hormones such as insulin, are avoided and food intake is distributed uniformly across the 40-hour wake period by providing hourly snacks. This approach, referred to as a constant routine protocol, allows for the assessment of the timing and amplitude of rhythms in many variables, within a relatively short period of time. Application of this method is less labor intensive than free-running or forced desynchrony studies, although still quite involved. This demonstrates that it is indeed not easy to assess endogenous circadian rhythmicity. The constant routine approach has revealed rhythmicity in nearly every variable ever studied. It also has revealed, by comparing the observed rhythmicity in the presence of a sleep–wake cycle to rhythmicity under conditions that the presence of a sleep–wake cycle induces and adds to endogenous circadian rhythmicity (Duffy & Dijk, 2002).

Entrainment of the human circadian clock

Given that endogenous circadian rhythmicity has been established in humans, a first question concerns the environmental variables that mediate synchronization of the human deep circadian pacemaker, which also influences sleep timing, to the 24-hour cycles of the rotating Earth. At first glance this question could be answered by sequentially removing all known rhythmic environmental variables until desynchrony is observed. In the real world, answering this question has, however, not been that easy.

LIGHT AND CIRCADIAN PHOTORECEPTION

Animal research has established that circadian pacemakers are located close to, or are well connected to, photoreceptive systems. Severing the connection between the photoreceptors and the circadian pacemaker will result in loss of synchrony between the behavioral and physiological rhythm and the 24-hour light–dark cycle. In mammals, including humans, the circadian pacemaker is located in the suprachiasmatic nucleus, which is connected to retinal ganglion cells by a monosynaptic pathway. It is now well established that it is indeed the light–dark cycle that is the main synchronizer of the circadian clock in humans as well. The evidence comes from many different approaches. These include laboratory experiments of exposure to light pulses and subsequent assessment of the timing of variables,

such as core body temperature and melatonin, that are considered reliable markers of the circadian pacemaker. These experiments have demonstrated that the timing of these physiological rhythms can be shifted by light exposure. The effects of the light pulses depend on the timing, duration, and intensity of the light. Light in the morning and afternoon hours, i.e., during the approximately 10-hour period following the core body temperature nadir, will advance the timing of rhythms. This means that on the days subsequent to a morning light pulse, melatonin will rise earlier. The advances are greatest for light pulses administered during the first 4 hours following the temperature nadir. Light pulses administered in the evening and nighttime hours before the core body temperature nadir will lead to a delay of these rhythms. These data can be summarized in phase response curves, and it has been established that all variables that are known to be under circadian control, including sleep propensity, can be shifted by light exposure. The magnitude of the phase shift depends on the intensity of the light in a logarithmic manner. Room light with an intensity of 100–200 lux, or even candlelight or a few lux, may already have a significant effect, but the effect of bright (1,000–2,000 lux) or daylight (50,000–100,000 lux) is two to three times greater. Phase shifts of up to 12 hours can be accomplished by 6 hours of timed light exposure for about three days (Duffy & Wright, 2005).

Despite the fact that laboratory experiments have indicated that light is considered the most important synchronizer of human circadian rhythmicity, the demonstration of the importance of light for sleep–wake regulation in the real world has not been straightforward. For example, in many blind individuals living in society, the sleep–wake cycle does cycle with an apparent 24-hour period. This is in part because the sleep–wake rhythm is determined not only by internal clock factors but also by social factors, and many of these blind individuals attempt to adhere to a socially dictated 24-hour sleep–wake cycle. Such a self-imposed sleep–wake cycle will induce apparent 24-hour rhythmicity in many variables—for example, in the core body temperature rhythm. It is only by long-term recordings of physiological variables such as core body temperature and sleep that it can be demonstrated that in these blind individuals physiological variables driven by the circadian clock are not synchronized to the Earth's rotation. Long-term recordings of subjective and objective sleep patterns have demonstrated that in many of these blind individuals, nocturnal sleep is periodically disrupted and during these periods daytime naps occur frequently (Lockley et al., 1997; Lockley et al., 2008). Simultaneous recordings of physiological markers of the circadian clock indicate that these periods of sleep disruption coincide with periods during which melatonin is secreted during the day rather than during the night. Whereas the sleep–wake patterns of these blind individuals confirm the importance of the light–dark cycle for entrainment, there is another group of blind individuals in whom the sleep–wake cycle and the melatonin rhythms are synchronized to the 24-hour day. In one group of blind individuals, this may be because the period of the circadian clock is sufficiently close to 24 hours to be synchronized by the weak synchronizing effects of the self-imposed 24-hour sleep–wake cycle. In another group of blind individuals, light may actually still reach the circadian clock, despite the lack of vision. This is because the effects of light on circadian rhythms are mediated in part by retinal ganglion cells that express the photopigment melanopsin. These ganglion cells, which project to the SCN, are directly sensitive to light and light of approximately 460–480 nm, i.e., blue light in particular. Thus in some blind individuals light can still shift the timing of circadian rhythms and can still acutely suppress the secretion of melatonin. It should be noted that these Intrinsically Photosensitive Retinal Ganglion Cells (IPRGCs) project not only to the SCN but also to the ventrolateral preoptic (VLPO) area in the anterior hypothalamus, which contains sleep active neurons and it is through this projection that light and blue light in particular is thought to exert its well-known alerting and performance-enhancing effects (Cajochen et al., 2005). Thus the timing, intensity and spectral composition of light shape our sleep–wake propensity rhythm through its effects on the timing of circadian rhythm and through its direct activating effects. These direct activating effects of light demonstrate that apparent sleep propensity is modulated by both internal factors, such as circadian phase, sleep debt and environmental factors, such as the intensity and spectral composition of light. The direct activating effects of light extend beyond alerting effects and include effects on fMRI and PET-assessed brain response to cognitive tasks (Vandewalle et al., 2009b).

Intrinsic period

We have discussed synchronization of the human circadian pacemaker and mentioned that under free-running conditions its period deviates from 24 hours.

How much does it deviate? How stable is this intrinsic period, and do individual differences in intrinsic period predict individual characteristics of sleep timing? A first question related to the deep oscillator is how its self-sustained oscillation can be best characterized. How stable is its period? Is it genetically determined? Does it change with age and does it predict interindividual differences in sleep–wake timing? Addressing these questions requires protocols that allow for an assessment of period that is not confounded by factors that are distinct from the deep circadian oscillator. Initial observations in healthy sighted individuals under classical free-running conditions in which the volunteers could choose when to go to sleep and had control over the light–dark cycle yielded estimates near 25 hours. It has since been recognized that given its sensitivity to light, assessment of the intrinsic period of the circadian clock should ideally be conducted in constant darkness, but this is not acceptable to sighted subjects. There are two alternative approaches. The first approach is to quantify the period of the circadian rhythms of blind individuals who are non-entrained, while living in society. The estimate of intrinsic period in this population is somewhat less than 25 hours. It has been argued that this estimate in not entirely unconfounded because the average does not include the periods of those subjects who are entrained, and it may be that these periods are closer to 24 hours than the periods of the free-running group. This estimate may also be confounded by feedback from the self-imposed 24-hour sleep–wake cycle and associated factors such as caffeine consumption. The second alternative approach is to minimize the confounding effects of light by distributing the effects over the circadian cycle. We have learned that light in the morning advances the clock, i.e., speeds it up, and light in the evening delays the clock, i.e., slows it down. By scheduling the sleep–wake cycle and associated (dim) light–dark cycle to a period far away from the circadian range, e.g. 20 or 28 hours, uniform distribution of light across the circadian cycle can be achieved. This is because the intrinsic period of the circadian clock is too close to 24 hour and too robust to follow these non-circadian sleep–wake schedules. Estimates of intrinsic period from these forced desynchrony protocols are on average 24.2 hours (Czeisler et al., 1999). Estimates from various physiological variables—e.g., melatonin, cortisol and core body temperature—are very similar and highly correlated, suggesting that one circadian pacemaker is driving all these rhythms. The estimates are also robust and are supposed to represent the best available estimate of intrinsic period yet. Several genes involved in the generation of circadian rhythmicity have been identified in mouse studies in particular. These genes include the Period genes, clock, NPAS2, BMAL1, the Cry genes and their involvement in sleep and other physiological processes is under intense investigation (Takahashi et al., 2008).

A first question about the circadian clock and sleep is: how does the intrinsic period of the circadian clock relate to sleep–wake timing?

Entrained phase

In healthy good sleepers living their normal lives, the circadian clock will not be free-running but synchronized, or entrained, to the 24-hour day–night cycle. Entrainment theory assumes that the difference between the intrinsic period and the 24-hour period is compensated for on a daily basis by light exposure in particular. Theoretically, the stable, synchronized (entrained) timing of the endogenous rhythms relative to the light–dark cycle depend on the magnitude of the mismatch as well as the strength of the light–dark cycle. Thus, in an individual in which the intrinsic period is 24.2 hours, the timing of the melatonin rhythm will be later when the subject is exposed to a weak light–dark cycle compared to a strong light–dark cycle. Furthermore, when two individuals are exposed to an identical light–dark cycle but the second subject's intrinsic period is 24.5 hours, then entrainment theory predicts that the entrained melatonin rhythm, even though synchronized to the 24-hour light–dark cycle, will be phased later. A final prediction is that when the deviation of the intrinsic period from 24 hours is greater than the maximal achievable daily adjustment, then the subject's circadian clock will not be synchronized to the 24-hour light–dark cycle. Assessment of intrinsic period is labor intensive and expensive and in only a few subjects have data on intrinsic period and entrained phase been obtained. As mentioned, entrained phase relates to the timing of endogenous circadian rhythms, such as the melatonin rhythm, relative to the light–dark cycle. In humans, light exposure consists of the natural light–dark cycle and artificial light. We will turn artificial lights on and off in synchrony with our sleep–wake cycle and a first estimate of the timing of the light–dark cycle can be obtained from the habitual sleep–wake cycle. It turns out that the timing of the rise of plasma melatonin in the evening relative to the onset of sleep is remarkably tightly associated with the

intrinsic period as assessed under desynchronized conditions. Please note that for the assessment of the endogenous rise of melatonin, subjects need to be studied in dim light conditions because light acutely suppresses melatonin. Data collected under these controlled conditions also show that minor differences in intrinsic period lead to considerable changes in entrained phase. Thus a difference in intrinsic period of as little as 15 minutes leads to a difference in the phase angle of the melatonin rhythm and habitual sleep time by as much as 1 hour (Gronfier et al., 2007).

Evidence that entrained phase is also determined by light exposure has also been obtained. Direct measurements of the light–dark cycle to which subjects are exposed have shown differences between early risers and late raisers, although it is not possible to identify the direction of the causality, i.e., if an early wake time causes an early light exposure or the other way around (Goulet et al., 2007). Additional evidence for the role of light in determining entrained phase, or at least the timing of wake time, comes from large survey studies. The timing of sleep in people living in rural areas appears to be more closely linked to the natural light–dark cycle than people living in large cities. This suggests that also in the real world, light is a determinant of entrained phase (Roenneberg et al., 2007).

Sleep–wake regulation: Interaction of circadian rhythmicity and sleep homeostasis

Our current thinking about sleep–wake regulation has been influenced to a considerable extent by the two-process model of sleep regulation (Borbély, 1982; Daan et al., 1984). In essence, it posits that sleep duration and sleep structure are governed by sleep homeostasis, allowing for recovery of lost sleep as well as being influenced by circadian clocks. What is the evidence that both of these processes contribute simultaneously to sleep timing and sleep structure?

Sleep displacement and the two-process model of sleep regulation

One approach to studying the interaction of sleep homeostasis and circadian rhythmicity consists of extension of wakefulness with recovery sleep initiated at other than habitual bedtimes. In one early experiment, wakefulness was extended from 16 to 20, 24, 28, 32, 36, or 40 hours with bedtimes at, 23, 3, 7, 11, 15, 19, and 23 hours (Åkerstedt & Gillberg, 1981). A key feature of the design of this influential study was that recovery sleep was not restricted and the subjects decided when to get up. Homeostatic regulation of sleep duration predicts a progressive increase in sleep duration when wake duration preceding sleep is extended from 16 to 40 hours. If sleep termination were governed solely by a circadian clock, then one may predict sleep to always terminate at 7 a.m. independent of the duration of wakefulness. The data show a complex pattern with an initial reduction in sleep duration for the first four conditions followed by a sudden increase when sleep is initiated at or after 15 hours. Now, how do we understand these data?

Borbély and colleagues proposed a model for the contribution of sleep homeostasis and circadian rhythmicity to explain these sleep displacement data as well as the sleep patterns observed during free-running conditions, including spontaneous desynchrony. In essence, it assumes that sleep pressure builds up during wakefulness and dissipates during sleep. The time course of this homeostatic sleep pressure was derived from measurement of SWA during baseline sleep and recovery sleep from 40 hours of sleep loss. The model assumes that sleep is terminated when this sleep pressure hits a lower threshold, which is modulated by the circadian pacemaker. This threshold is higher during the biological day than the biological night and, as a consequence daytime sleep duration is short even when wake duration is relatively long. This model and its successors have generated many research questions. Are all aspects of sleep, such as SWS, REM sleep, and sleep spindles, influenced by sleep homeostasis and circadian rhythmicity? What does the circadian sleep propensity rhythm look like and what is the relative contribution of sleep homeostasis and circadian rhythmicity to sleep propensity? Does the circadian clock influence sleep homeostasis or does sleep homeostasis influence the clock? How can we investigate the separate contributions of these two sleep regulatory processes?

Forced desynchrony of sleep–wake cycle and circadian rhythmicity

Quantifying the contribution of sleep homeostasis and circadian rhythmicity to aspects of sleep regulation requires that sleep occurs at all circadian phases and that at the same time homeostatic sleep pressure at sleep onset can be quantified. This can be achieved in a variety of protocols, an essential feature of which is that the period of the sleep–wake cycle is much shorter or much longer than 24 hours. Weitzman and colleagues used 3-hour sleep–wake cycles;

Carskadon and others used very short 90-minute 'days'. More recently, 20, 28, and 42.85 hours have been used (see Figure 2.7). Because in these protocols the ratio of wakefulness to sleep in general is kept to 2:1, sleep episode duration varied from 0.5 to 14 hours or so. Whereas the short sleep episodes allow an assessment of the circadian variation of the ability to initiate sleep, long sleep episodes are required to study the dynamics of the sleep process at all circadian phases. When the sleep episodes are sufficiently long, it is also possible to study the relative contribution of sleep-dependent and circadian processes. The analysis of the circadian influence on data collected in these protocols requires that each observation is assigned a circadian phase. This requires the assessment of reliable circadian markers such as core body temperature or melatonin. The analysis of sleep–wake homeostasis on the data collected requires that each observation is assigned a homeostat coordinate. This is accomplished by determining the duration of wakefulness or sleep preceding the time point at which an observation was made.

TIME COURSE OF SWS/SWA: HOMEOSTATIC AND CIRCADIAN ASPECTS

SWS/SWA are considered markers of the sleep-homeostat driven by the sleep–wake cycle independent of the circadian cycle. It is therefore predicted that SWS/SWA decline during all sleep episodes and that the level of SWS/SWA is high at the beginning of sleep and at similar levels independent of circadian phase provided that wakefulness preceding sleep for these sleep episodes is similar. This prediction has been confirmed by PSG analyses in sleep-displacement studies, spontaneous desynchrony studies and forced-desynchrony studies. The latter data indicate that there is a minor circadian modulation of SWA at the beginning of sleep, but when comparing the sleep-dependent and circadian component the predominance of the homeostatic component is very evident (Dijk & Czeisler, 1995) (see Figure 2.8). The implication is that both the buildup of homeostatic sleep pressure during wakefulness and its expression as SWA during sleep are not markedly affected by a circadian process. Please note that when we consider the duration of NREM sleep (i.e., the duration of the sum of the stages 1, 2, 3, and 4, expressed as % of TST), in addition to a sleep-dependent modulation, a circadian modulation becomes apparent. The crest of the circadian modulation is located at a circadian phase corresponding to approximately 10 p.m., and the minimum at 8 a.m.

CIRCADIAN MODULATION OF SLEEP SPINDLES

Given the different neurophysiological basis of slow waves and sleep spindles, it may not be surprising that their circadian and sleep-dependent regulation differs to a considerable extent. In contrast to slow waves, sleep spindles are to a considerable extent under circadian control (Dijk & Czeisler, 1995). Quantification of both total EEG activity in the frequency range of sleep spindles, as well as of parameters of sleep spindles—such as their density, amplitude and frequency—have revealed a crest in spindle activity during the circadian night, in close association with the melatonin peak and falling limb of the temperature rhythm (Dijk et al., 1997; Dijk & Czeisler, 1995; Wei et al., 1999). During sleep at night the frequency of sleep spindles is lower, i.e., the average frequency shifts from approximately 13.25 Hz when sleep occurs during the biological day to 12.75 Hz during the biological night. At the same time the duration of spindles increases, the number of spindles increases and their amplitude is greater. Sleep spindle characteristics also show a sleep-dependent regulation. Spindles become faster and longer as sleep progresses. Sleep spindles are of interest because they have been implicated in the consolidation of memory, in particular on procedural tasks but also on declarative memories. Sleep spindles have been implicated in blocking the transfer of sensory information at the level of the thalamic relay nuclei, thereby contributing to the consolidation of sleep. It is also of interest that sleep spindles decline with age and are enhanced by hypnotics that interact with the $GABA_A$-BDZ receptor complex and it has been argued that the circadian modulation of sleep spindles represents an endogenous circadian hypnotic signal (Dijk et al., 1997; Knoblauch et al., 2003).

CIRCADIAN MODULATION OF REM SLEEP: A GATE TO AND FROM WAKEFULNESS?

In contrast to SWS, REM sleep is under strong circadian control. Evidence for this has been derived from PSG analyses of sleep during free-running studies, spontaneous desynchrony studies and forced desynchrony studies. The crest of the REM sleep propensity rhythm, as assessed as REM sleep expressed as a % of TST, is located 1–2 hours after the core body temperature nadir. REM sleep propensity can also be assessed by measuring the latency to REM sleep. The distribution of REM latency is bimodal, with a first peak in the distribution for latencies around 20 minutes and a second peak around 50–110 minutes. REM latencies belonging

to the first peak in the distribution are referred to as sleep-onset REM episode. When sleep is initiated around the core body temperature nadir, sleep-onset REM episodes are very frequent (Czeisler et al., 1980b). Sleep-dependent regulation of REM sleep is characterized by what has been coined the sleep-dependent disinhibition. REM sleep appears somewhat inhibited at the beginning of sleep, particularly in young individuals who have much SWS and then its propensity increases as sleep progresses (Dijk et al., 1999). The sleep-dependent disinhibition is also observed in phasic events, such as the density of rapid eye movements (Khalsa et al., 2002). Because of the predominance of the circadian regulation of REM sleep, the time course of REM sleep in the course of a sleep episode very much depends on the circadian phase of sleep onset. REM sleep declines as sleep progresses when sleep is initiated on the rising limb of the core body temperature rhythm. In contrast, REM sleep increases as sleep progresses when sleep is initiated on the falling limb, as is the case during entrainment. This polarity is of interest because most spontaneous awakenings occur from REM sleep and the combination of the sleep-dependent and circadian regulation of REM sleep results in a sharp peak in REM sleep propensity at habitual wake time. REM sleep indeed has been considered a gate to wakefulness (Lavie, 1986) and awakening from REM sleep leads to less sleep inertia than awakening from stage 2 sleep (Silva & Duffy, 2008). Paradoxically, it is also at this circadian phase that circadian sleep propensity is greatest and, maybe, REM sleep should be considered both a gate from and to sleep.

SLEEP INITIATION AND SLEEP TERMINATION: A PARADOXICAL RHYTHM OF CIRCADIAN SLEEP–WAKE PROPENSITY

The circadian and homeostatic regulation of sleep structure occurs within a sleep episode, the initiation and duration of which is also under the control of these two processes. During spontaneous desynchrony, sleep termination occurs almost exclusively on the rising limb of the CBT rhythm. Sleep initiation preferentially occurs on the falling limb of the CBT rhythm or on the middle part of the rising limb. In the latter case, sleep episodes can be very long—up to 18 hours. Interestingly, sleep is rarely initiated in the early evening hours and this phase has been referred to as the wake maintenance zone (Strogatz et al., 1987) or forbidden zone for sleep (Lavie, 1986). Please note that during spontaneous desynchrony, the very long sleep episodes that are initiated on the rising limb will continue throughout this wake maintenance zone. Thus it may be more appropriate to consider this phase as a time during which it is difficult to initiate sleep. During spontaneous desynchrony, the assessment of the circadian sleep propensity rhythm is confounded by the variation in wake duration preceding sleep. Assessments of the circadian sleep propensity rhythm in forced desynchrony are less affected by this confound. The circadian rhythm of sleep propensity as assessed by sleep initiation is very pronounced, with peak, i.e., shortest sleep latencies, at approximately 0–2 hours after the temperature nadir. Longest sleep latencies are observed 10–8 hours before the temperature nadir. Under conditions of entrainment, these circadian phases correspond to a maximum propensity to initiate sleep at 6–8 a.m. and a minimum likelihood to initiate sleep at 8–10 p.m. In other words, the circadian drive for sleep is greatest around habitual wake time, and the circadian drive for wakefulness is greatest around bedtime. Assessment of the circadian rhythm of the propensity to terminate sleep can be derived on the basis of TST as well as assessment of wakefulness, i.e., sleep disruption, in the last part of the sleep opportunity. The waveform of the propensity to terminate sleep is just the opposite of the waveform of sleep initiation. In other words, the circadian drive for wakefulness as assessed by disruption of sleep consolidation is greatest in the wake maintenance zone. The circadian drive for sleep as assessed by the continued consolidation of sleep is greatest near the crest of propensity to initiate sleep. Thus there is no apparent need to postulate separate circadian drives for sleep initiation and sleep termination (Dijk & Czeisler, 1994).

We are still left with the paradoxical observation that the circadian drive for wakefulness is greatest near sleep onset and the circadian drive for sleep is greatest at the end of the habitual sleep episode. Review of relevant data from many different protocols confirms the consistency of this rhythm, provided that the homeostatic drive for sleep is controlled.

CONSOLIDATION OF SLEEP AND WAKEFULNESS THROUGH INTERACTION OF H AND C

The paradoxical phase relationship between the timing of the habitual sleep–wake cycle and the circadian sleep propensity rhythm can be understood when we consider that both the sleep homeostat and the circadian pacemaker contribute to sleep timing and sleep continuity. When sleep consolidation is plotted as a simultaneous function of circadian phase

and time since the start of the sleep episode, it becomes clear that a full 8 hours of sleep consolidation can be accomplished only when sleep is initiated just after the wake maintenance zone. Homeostatic sleep pressure dissipates as sleep progresses, but this does not lead to sleep interruption because the circadian drive for wake dissipates and turns into a circadian drive for sleep. It is only at the inflection point of the circadian sleep–wake propensity rhythm that sleep is then terminated. In contrast, when sleep is initiated just after habitual wake time, initially sleep consolidation is high because of the high homeostatic sleep pressure, but as soon as this dissipates, sleep is interrupted because the circadian drive for wakefulness increases. Thus a precise alignment of the sleep–wake homeostat and circadian rhythms is essential for sleep consolidation. If the circadian wake maintenance zone occurs too late, the strong circadian arousal signal may prevent sleep initiation at socially accepted times and the subject may postpone bedtimes. If the homeostatic drive for sleep is too weak, both sleep initiation and consolidation may be compromised. A precise alignment and well-balanced contribution of the sleep–wake homeostat and circadian sleep–wake propensity rhythm is essential not only for sleep consolidation but also for wake consolidation (Dijk et al., 1992; Dijk & Czeisler, 1994; Wyatt et al., 1997; Wyatt et al., 1999). In the opposing process model of sleep regulation, which can be considered a variation of the two-process model, a primary role of the circadian arousal signal is to consolidate the wake episode in the presence of the buildup of homeostatic sleep pressure (Edgar et al., 1993). Indeed, when the SCN is lesioned, as can be done experimentally in squirrel monkeys, and the circadian arousal signal is no longer present, the wake episodes become highly fragmented. In humans, the contribution of the circadian arousal signal to sleep propensity and waking performance has been analyzed in FD protocols. The laboratory data show that performance and alertness can be maintained only throughout a 16- to 18-hour wake episode if the alignment with the circadian rhythm of arousal is as under entrained conditions (Wyatt et al., 1999). When we extrapolate these findings to the real world, the following scenarios emerge. The day-shift worker will wake along a trajectory on which the circadian drive for wakefulness opposes the increase in homeostatic sleep pressure during the working period and for most of its leisure period. In contrast, alertness and performance in the night-shift worker, waking up in the afternoon, will initially be supported by the circadian drive for wakefulness. As the night shift starts, the already considerable homeostatic sleep pressure will no longer be opposed by the circadian arousal rhythm, and performance will be compromised. In fact, at approximately 7 or 8 a.m., coinciding with the end of the night shift/commute home, the combination of high homeostatic sleep pressure and lack of circadian drive for wakefulness is such that performance is most compromised. Evidence that the interaction between circadian rhythmicity and sleep homeostasis determines performance and alertness in individuals living in their habitual environment has been obtained in blind individuals (Lockley et al., 2008).

CONTRIBUTION OF MELATONIN TO CIRCADIAN REGULATION OF SLEEP–WAKEFULNESS: PHASE SHIFTING AND SILENCING OF WAKE-PROMOTING CIRCADIAN SIGNALS

Both core body temperature and plasma melatonin have been used extensively as markers of circadian phase and the circadian sleep–wake propensity rhythm displays a close temporal association with both. To what extent these physiological variables and underlying processes play a causal role in circadian sleep–wake regulation has been investigated, particularly for melatonin (see Figure 2.9). Melatonin's role in circadian sleep–wake regulation has been related to its direct sleep-inducing/facilitating effects and its effects on shifting the timing of circadian rhythm (Arendt, 2006; Srinivasan et al., 2009). The latter role is relevant in the context of the question whether the human circadian pacemaker be synchronized by 24-hour cycles of pharmacological or non-pharmacological manipulations other than light. An answer to this question is obviously relevant to the traveller who frequently crosses multiple time zones, the shift worker and the non-entrained blind individuals. To date the only known manipulation for which this has been established unequivocally in humans is the timed administration of exogenous melatonin. Similar to light, a phase response curve for melatonin has been established. There are important differences between the effects of light and melatonin. Whereas light exposure in the evening delays circadian rhythms, melatonin administration in the evening advances circadian rhythms. Whereas light exposure in the morning advances circadian rhythms, melatonin administration at this time does not seem to substantially delay circadian rhythms. Overall, the effects of melatonin which are presumably mediated by melatonin receptors in the SCN, are much more modest than the effects of light. The effects of

melatonin are not limited to phase shifting effects. Just as the direct alerting effects of light, melatonin has direct sleep-facilitating effects. These effects have been demonstrated in a variety of protocols including daytime naps protocols (Nave et al., 1995), forced desynchrony protocols (Wyatt et al., 2006) and extended sleep opportunity protocols (Rajaratnam et al., 2003; Rajaratnam et al., 2004). In the latter protocols subjects were instructed to be in bed for 16 hours per 24-hour period with lights out at 4 p.m. and lights on at 8 a.m. This bedtime starts well before the endogenous rise of the melatonin rhythm. Subjects were exposed to this extended sleep schedule for nine days on two occasions. On one occasion, melatonin was administered at lights-out of all extended sleep episodes except the last one. In the other condition, placebo was administered at lights-out of all extended sleep episodes and sleep was recorded throughout the protocol. In addition, constant routines prior to and following this schedule were used to assess endogenous circadian rhythmicity. If melatonin plays a physiological role in sleep–wake regulation, then administration of melatonin should lead to an improvement of sleep during the daytime (i.e., when endogenous melatonin levels are low). The question then arises of what will happen to sleep during the nighttime hours. Will subjects continue to sleep, or will homeostatic sleep pressure have been dissipated? The data show that melatonin administration indeed results in an increase in sleep efficiency during the daytime. When assessed over the entire 16-hour sleep opportunity, total sleep time was not significantly different between the placebo and melatonin condition and asymptoted to 8.7 hours. Analysis of the endogenous circadian rhythms of cortisol, melatonin, and body temperature indicated that melatonin administration led to an earlier timing of all of these rhythms by as much as 2–3 or more than after placebo. Data from this experiment and many others demonstrate that melatonin has both circadian phase-shifting effects (in particular phase-advancing effects) and direct sleep-facilitating effects. The effects are thought to be mediated by melatonin receptors in the suprachiasmatic nucleus, the locus of the biological clock in humans. The direct sleep-facilitating effects have been interpreted as a silencing of the wake-promoting signal from the biological clock. It is the combination of phase shifting and sleep-facilitating effects that makes melatonin useful in the treatment of sleep timing disorders in, for example, blind individuals but also in delayed sleep-phase syndrome.

CONTRIBUTION OF OREXIN TO CIRCADIAN REGULATION OF SLEEP–WAKEFULNESS

The peptide orexin, also referred to as hypocretin, was discovered by looking for transcripts that were selectively expressed in the hypothalamus, the brain area essential to the maintenance of homeostasis and circadian rhythmicity. Hypocretin neurons are located in the lateral hypothalamus and project to numerous brain areas, including brain stem nuclei that play a key role in sleep–wake regulation. It is an activating neurotransmitter system thought to play an important role in the consolidation of vigilance states and maintenance of wakefulness in particular. In the squirrel monkey, concentrations of orexin in cerebrospinal fluid increase in the course of the waking day, and this increase is thought to be driven by suprachiasmatic nucleus and activity. Deficiencies in orexin are associated with excessive sleepiness and cataplexy, typical for the sleep disorder narcolepsy (Fronczek et al., 2009).

Individual differences in homeostatic and circadian regulation of sleep–wake cycles in healthy men and women: Physiology and genes

The concept of sleep–wake regulation through interaction of circadian and homeostatic processes provided a powerful framework for the study of sleep at both the group and individual levels. The multiple phenotypic aspects of sleep vary between individuals, and many of these individual differences are stable over time and across conditions. Such stable, trait-like differences often (but not always) have a genetic basis, and the study of individual differences may provide new insights into the mechanisms underlying normal and pathological variation in sleep. In recent years, some of the individual differences in sleep have been studied in some detail, and in a few cases some of the interindividual differences have been linked to variations in specific genes.

Deep sleep/shallow sleep: Slow waves and other EEG oscillations

The EEG plays an important role in sleep research. Marked differences in EEG characteristics exist between individuals and it was recognized early on that the EEG is among the most heritable characteristics. SWS and slow oscillations differ between individuals, and these differences are very stable across conditions in which sleep regulatory systems are differentially activated, for example, baseline sleep and recovery from sleep deprivation. The magnitude of

these interindividual differences is considerable. In fact, the interindividual differences in SWS are much greater than the differences induced by sleep deprivation (Tucker et al., 2007). Some of these interindividual differences in SWS are attributable to known factors such as the age and sex of the subject. Starting during adolescence, SWS and SWA exhibit a marked decline throughout the life span and throughout the life span women have more SWS/SWA than men (Carrier et al., 2001). But even within a relatively narrow age group of only men or women, differences in SWS and SWA persist. Some of these differences have been related to variation in genes. Thus a polymorphism in the gene coding for adenosine deaminase, which leads to reduced breakdown of adenosine, has been linked to increased SWS and SWA. Furthermore, a polymorphism in a gene coding for the adenosine 2A receptor has also been shown to associate with changes in SWS and SWA (Landolt, 2008). These associations are consistent with our current views on a role for adenosine in sleep regulation. SWS and SWA are also affected by a polymorphism in PER3, which is one of the genes involved in circadian rhythmicity (see below).

Individual differences in the EEG are not limited to slow waves but have also been reported for sleep spindles and higher-frequency activities such as beta activity, for which the estimated heritability is 96% (De Gennaro et al., 2008). For most of these individual differences, associations with variations in specific genes have not been identified. A polymorphism in the gene coding for the enzyme catechol-O-methyltransferase (COMT), which plays a significant role in dopamine metabolism, leading to changes in alpha activity in the EEG during sleep (Bodenmann et al., 2009).

One key question in the research on interindividual differences in sleep regulation, including SWS and the EEG, is how these differences relate to differences in sleep regulatory processes. For example, do differences related to either genes or age in SWS simply reflect differences in EEG generating mechanisms with no link to sleep homeostasis, or do these differences indeed imply differences in sleep intensity and sleep need? To answer these questions, individuals who differ with respect to these sleep characteristics will have to be studied under conditions in which the sleep regulatory processes are challenged and correlations between these heritable characteristics and outcome measures such as sleep quality, sleep depth, and waking performance are assessed.

Long sleep/short sleep

The notion that some of us are short sleepers and others are long sleepers is widespread and the statement that we sleep for 8 hours or so after 16 hours of wakefulness is certainly not true of the population of good sleepers in general.

Several studies on the distribution of sleep duration show that reported sleep duration is 7.0 hours with a standard deviation of 1.5 hours (Groeger et al., 2004). This normal distribution implies that many factors (genes) contribute to sleep duration and that indeed some of us fall within the extremes on either end of the distribution. Age is again a major contributor to this variation, with children, adolescents, and young adults sleeping considerably longer than middle-aged and healthy older adults. Within the age group of young adults, short and long sleepers have been studied in the laboratory. A consistent finding across these studies is that SWS is preserved in short sleepers, or may even be slightly enhanced. REM sleep is curtailed. The response to sleep deprivation differs between short and long sleepers, such that long sleepers show more of an increase in SWS/SWA than short sleepers. Quantification of this response to sleep deprivation suggests that this may be related to a lower level of SWS at baseline in long sleepers, which leaves them more room for an increase (Aeschbach et al., 1996). Short and long sleep is also associated with changes in circadian organization. In the absence of the sleep–wake and light–dark–cycle—i.e., during constant routine conditions—the biological night, indexed by the rhythm of melatonin and other physiological markers, is shorter in short sleepers than in long sleepers (Aeschbach et al., 1996; Aeschbach et al., 2003). Whether this circadian difference is causing the differences in sleep duration or is a consequence of the short period of darkness and longer period of light short sleepers have exposed their circadian system to remains unclear. Recently, two short sleepers were shown to carry a point mutation in yet another circadian gene, Dec2. When this genetic variation was introduced in mice and fruit flies, somewhat shorter sleep duration was observed in these species as well, suggesting that this mutation in a circadian gene could contribute to the regulation of sleep duration (He et al., 2009). One major question in the study of short and long sleepers is to what extent short sleepers are better at tolerating the increases in sleep pressure associated with wakefulness or whether there is a slower build-up of homeostatic sleep pressure in short sleepers. Much of the evidence to date favors the

former interpretation. Thus short sleepers display more EEG signs of drowsiness during wakefulness, i.e., more theta activity. When habitual sleep duration is quantified through actigraphy and sleep diaries and sleep propensity is then assessed in the laboratory by assessment of daytime sleep latencies or total sleep time in extended sleep opportunities, short sleepers show signs of a sleep debt, i.e., their sleep latencies are shorter and the rebound in TST is greater. Thus the endophenotype of short and long sleepers may be more complicated than just a difference in sleep need. The data show that adequate phenotyping of individuals who differ with respect to reported sleep characteristics is essential for identifying the sleep regulatory processes that are affected. As such, better phenotyping is also required to interpret age-related changes in sleep structure, sleep propensity, and sleep duration. Whereas healthy older people sleep less at baseline, with less SWS and reduced sleep consolidation, this does not lead to an increase daytime sleep propensity. In fact, older people are less sleepy than young adults, and when given 16 hours of sleep opportunity per 24 hours for several days, older people sleep only 7.5 hours, whereas young adults sleep 8.9 hours (Klerman & Dijk, 2008). Thus age-related reduction in sleep duration indeed appears to reflect a reduction in sleep need, in contrast to the reduction in habitual sleep duration experienced by many young adults, which most likely reflects sleep restriction.

Early sleep/late sleep: Chrono- or homeotypes?

Another phenotype that attracts much attention is the owl vs. the lark phenotype. Variation in sleep timing is considerable indeed Some of us go to sleep when others wake up. Just like for some of the other individual differences we discussed, aging is a major explanatory variable. Whereas teenagers and young adults sleep late, older people sleep and wake early. Furthermore, there are sex differences as far as sleep timing is concerned. Women tend to wake slightly earlier than men. As with the previously discussed characteristics of sleep, variation in the preferred timing for sleep and waking activities, also referred to as chronotype, differs even within a narrow age range. Laboratory studies have shown that early sleepers are also characterized by earlier rhythms of body temperature and melatonin as well as earlier timed cycles of the expression of clock genes in leukocytes (Archer et al., 2008; Duffy et al., 1999; Mongrain et al., 2004; Mongrain et al., 2006a) (see Figure 2.10). In addition, assessment of endogenous circadian period in forced desynchrony protocols has shown that ratings on the morningness–eveningness questionnaires indeed correlate with entrained phase and intrinsic period of circadian rhythms (Duffy et al., 2001). The clock runs fast in early birds. Whereas these associations are in full agreement with the prevailing view of the role of circadian rhythmicity in sleep timing, analysis of PSG recorded sleep has shown that aspects other than the timing of sleep are also affected by chronotype. It has been reported repeatedly that morning types have more SWS and SWA, in particular in the first NREM cycle and a faster decline of SWA during sleep (Kerkhof, 1991; Mongrain et al., 2006b). Furthermore, increases in signs of drowsiness in the EEG during wakefulness appear to be faster within morning types (Taillard et al., 2003). Within the conceptual framework of the homeostatic and circadian regulation of sleep, you may go to sleep and wake early because your clock is set early or the buildup and dissipation of sleep pressure is fast. The data indicate that both pathways contribute to the observed phenotypes. Clock genes are obvious candidates to contribute to variation in chronotype. So far, the clock genes PERIOD2 as well as CKI delta, genes coding for enzymes involved in phosphorylation of clock proteins, have been implicated in abnormally early sleep (Toh et al., 2001; Xu et al., 2005). Variation in the clock gene CLOCK and PER3 has been associated with variation in chronotype (Archer et al., 2003; Lazar et al., In press). The contribution of the variable number tandem repeat polymorphism in PER3 to circadian rhythmicity and sleep physiology has been investigated in a prospective study in which subjects were selected only on the basis of their genotype, independent of chronotype or any other sleep characteristic (Viola et al., 2007). It was found that whereas the polymorphism didn't affect circadian phase, it did affect SWS, SWA and the increase of theta activity during wakefulness. Furthermore, cognitive decline during sleep deprivation, and in particular during the early morning hours, was much more severe in the subjects homozygous for the allele previously associated with morningness. A subsequent fMRI study revealed that the gene predicted an altered dynamic in the brain responses during an executive task in the course of a normal sleep–wake cycle and a night of sleep deprivation (Vandewalle et al., 2009a). The data demonstrate that the effects of polymorphisms in clock genes associated with individual differences in sleep timing are associated with changes that go well beyond

changes in the timing of rhythms and affect many aspects of sleep physiology (Dijk & Archer, 2009).

Homeostatic and circadian regulation of sleep: Summary and implications for the understanding of sleep disorders

It is well established that sleep is regulated through a fine-tuned interaction of circadian and homeostatic processes. These two processes emerge from and affect multiple physiological and molecular processes and concern many aspects of sleep and wakefulness. Disruption of the phase relationship between the homeostatic and circadian process as well as changes in the strength of homeostatic sleep pressure and circadian drive for wakefulness and sleep lead to disturbance in sleep and alertness and other aspects of physiology. Sleep homeostatic mechanisms and circadian processes can be manipulated by a variety of behavioral, environmental and pharmacological interventions, may be used to improve sleep and wakefulness. Emerging knowledge about interindividual differences in sleep–wake regulation and the identification of the underlying genomic variation provides for new avenues in sleep research and holds promise for the development of individualized treatment paradigms.

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CHAPTER

3 The Functions of Sleep

Yvonne Harrison

Abstract

The drive for regular sleep is present in many, if not all, species and is assumed to be under the control of homeostatic and circadian systems, developed in response to a need to adjust to geophysical (climatic, seasonal, and environmental) features of the environment. Given that so much study time has been invested in the assumption that to take away the opportunity for sleep will reveal the very essence of the need for that process, very few researchers have questioned the validity of this approach. Yet sleep loss, for many species, is costly and stressful, and in the laboratory setting the emotional or motivational components of cognitive deficits remain largely unmonitored. An evolutionary approach to understanding the functions of sleep assumes that clues lie in studying differences in how sleep has developed between species and under differing environmental conditions. This approach has provided important insight, but there are difficulties in making comparisons between species of widely differing physiological makeup and complexity. Interest in the relationship between sleep and memory processes has grown rapidly in recent years, and there is a sense that we have reached a breakthrough in our understanding of the functions of sleep. However, while key researchers argue that sleep is an essential state for optimal efficiency in the processing of memory, others remain unconvinced and see sleep as, at best, favorable but not essential to the consolidation and enhancement processes presumed to underpin memory.

Keywords: sleep, homeostatic, circadian, environmental factors, memory, emotion

Introduction

Ask children why sleep is important and they are likely to tell you that sleep is something they have to do every night if they are to grow into strong, healthy adults. Ask their parents why sleep is important and their explanation is likely to be along the lines of needing sleep for physical health, vitality, and general well-being. This assumption is mirrored in commonly held beliefs about sleep; when asked if they would like to have more sleep, about half of over 10,000 respondents to a recent Internet survey said they would, but this was related to perceived stress rather than reported daytime sleepiness (Anderson & Horne, 2008), and while Groeger et al. (2004) failed to find compelling evidence of a substantial decline in sleep duration over recent years in the British public, when sleep difficulties were reported these were again related to difficulties encountered in daily life. So there is a general feeling that sleep does something important for us, and that we need to get enough or there will be some cost, but we are not quite sure what or why that is.

However, look to the scientific literature for an explanation of why we sleep, and the story is not that much clearer. Despite extensive efforts over the last 100 years or so, our understanding of the functions of sleep is far from complete. The question of why we sleep has been approached from a number of angles; some researchers compare species and ask how sleep has developed differently in individual animals and for what apparent benefit. Others might look to changes in sleep patterns within the

same species over a lifetime, or perhaps consider the effects of abstinence from sleep in either the long or short term. Whatever the approach, a number of questions remain central to the debate. To what extent is sleep purely an adaptive function with little or no physiological purpose? Is sleep a process that, although costly in time, adds something positive to the likely survival of a species? Why is it that some animals appear to function quite well without sleep for long periods of time and that, even in humans, the effects of sleep loss are far from dramatic? To what extent is sleep a restorative process? What is the role of the NREM rebound that, although not universal, is an effect common to many animals following periods of sleep abstinence, and strong evidence in support of a homeostatic role for sleep? What about individual roles for NREM and REM sleep, or perhaps changing roles across the life span or different environments? In reviewing these approaches, the aim of this chapter is to provide some insight into current theories of how sleep has evolved over time and across species, and to ask what purpose sleep might continue to have in modern, everyday life.

This chapter will first explore the arguments concerning the emergence of sleep specifics, in particular the role of REM and NREM sleep, before then asking to what extent these ideas have contributed to our current knowledge of the functions of human sleep. Two quite different positions will be explored: The first assumes that sleep serves a vital function in the integration of sensory input with memory structures and processing (cf. Kavanau, 2005, 2006; Walker, 2005). The second holds that sleep performs no single, clearly discernible vital function other than to inhibit wake and that, when the need arises, many species function perfectly well without some, if not all, of their normal quota of daily sleep (Horne, 2006; Rial et al., 2007; Vertes, 2005; Vertes & Siegel 2005).

The evolution of sleep

The rationale behind an evolutionary approach to understanding sleep processes assumes that if we understand something of the environmental and functional conditions that determined the emergence of a particular process, such as sleep, then we can go some way toward understanding current processes and functions more clearly (Nicolau et al., 2000). Many researchers interested in the evolution of sleep hold the view that at some point in the history of the planet it was inhabited by animals with no need for sleep. It follows that something must have favored the emergence of sleep, whether biological, environmental, or behavioral, and in doing so offered a value to that species in terms of long-term survival that outweighed the cost of immobilization, loss of awareness, and, for some, increased risk of predation. Kavanau (2004, 2006) suggests that this event can be traced to the development of complex visual apparatus and the concurrent increasing demands placed on limited neuronal circuitry. It is argued that while developments in the properties of the visual system added immense value in terms of species survival (the ability to process a complex visual field to a greater level of acuity, allowing for increased speed and accuracy of motor response), this required greater volume and/or complexity of existing neuronal structures.

In particular, animals for the first time were able to form and store memories, which reflected the complexity of their developing sensory systems and behavioral challenges. One solution to this emerging conflict, suggested by Kavanau (2004, 2006), is the development of multifunctionality of neuronal systems and circuitry, in which the same area of the brain is able to engage and contribute to more than one process, thereby circumventing some of the difficulties of limited physical brain matter or space within the cranium. Multifunctionality, while highly efficient, is a property that persists across many species to this day. Kavanau's (2004, 2005, 2006) work has proved to be very influential in recent years. On the one hand it provides an intuitively appealing picture of the emergence of sleep in prehistoric times as a response to the emergence of more complex physical and cognitive attributes of a species, while also going some way toward explaining current popular ideas about sleep function in humans, in particular the role of sleep in the processing of memories. This is an idea that has gathered considerable momentum over the last 10 years or so of research.

One clue as to the reasons underpinning the emergence of sleep might lie with the distinction between REM and NREM sleep. Although early psychologists engaged in the study of sleep deprivation, such as Patrick and Gilbert (1896), observed that sleep was not a uniform state throughout the night, perhaps amazingly the classification of sleep into two distinct states of NREM and REM sleep was not made until the 1950s, with the landmark discovery of REM sleep (Aserinsky & Kleitman, 1953). We are now well accustomed to the division of sleep, at least in land mammals, into alternating periods of NREM and REM cycles, with clearly

discernible neurophysiological and behavioral patterns of activity. In humans, these states are very different. NREM sleep is characterized by increasing levels of slow, synchronized, high-amplitude features of the EEG and decreased (relative to wake) blood flow in the prefrontal and parietal cortices, thalamus, hypothalamus, basal forebrain, basal ganglia, cerebellum, anterior cingulate cortex, precuneus, and mesiotemporal cortices (Maquet, 2000; Taber et al., 2006). During this sleep, which, particularly later stages 3 and 4, we typically think of as deeper stages of sleep, responsiveness to external stimuli is low and arousal less likely.

In contrast, REM sleep is a period of fast, mixed, low-amplitude EEG and increased (relative to wake) activation of the thalamus, pons, limbic structures, and occipital cortex but reduced (relative to wake) activity in the frontal and parietal areas (Maquet, 2000; Taber et al, 2006). In addition, during REM we see a metabolic rate similar to wake, increased variability of heart rate and respiration, loss of muscle tone producing an effective flaccid paralysis, and rapid eye movements. Accounts of narrative dreams are far more likely during this state then during NREM sleep and arousal more likely toward the end of a period of REM sleep. A lack of uniformity amongst researchers and across disciplines led to the use of a number of alternative descriptors for these states, including quiet vs. active sleep, paradoxical sleep, and D-sleep. This was addressed to a great extent by the standardized classification developed by Rechtschaffen and Kales (1968) and since widely adopted, but some early terminology persists to this day and remains appropriate, particularly where the criteria developed for the identification of NREM and REM states in adult human sleep may not be generalizable. This is the case in the study of human infants, where we are left with the distinction between quiet and active sleep, often purely for pragmatic reasons, and based to a great extent on observable behavioral state changes. Many researchers have also questioned whether it is reasonable to apply these criteria when searching for evidence of different sleep states in other animals, particularly insects and reptiles (Siegel, 2008).

Taylor et al. (2000) reminds us that within an evolutionary approach we should always look for small changes when investigating the emergence of physiological processes, such as sleep states. With that in mind, these authors advocate that as REM sleep is more similar to the waking state, this is the type of sleep that is most likely to have emerged first. There is a lack of consensus on this point, and in fact many researchers advocate the contrary position that NREM sleep is the first to emerge. So what are the arguments in favor of the REM-first position?

If we look to animals assumed to retain many of the features of their primitive ancestors, then the evidence is mixed. On the one hand, from the limited study of monotremes (egg-laying mammals), we have the often-cited example of the echidna, which appears to experience no REM sleep at all, to the recent and contradictory finding of high levels of REM sleep in the duck-billed platypus (Siegel et al., 1998, 1999)—more on the importance of this finding later when returning to a discussion of Kavanau's theory of sleep and memory. Along similar lines, Taylor et al. (2000) point toward the unexpected finding of REM sleep in some reptiles. Secondly, in favor of the REM-sleep-first position, we are asked to consider the ability to regulate internal body temperature (homeothermy), which is known to develop later in evolutionary terms. This does not happen during REM sleep, and so it is argued that there is no adaptive advantage to the emergence of a sleep state that is characterized by an earlier feature, i.e., to take a backward step in terms of sustainability. Thirdly, Nicolau et al. (2000) wonder whether the high proportion of REM sleep in mammalian young is an expression of the recapitulation theory in which individual early development is assumed to follow the pathway of evolutionary species development.

While Taylor et al. (2000) come down firmly in the REM-sleep-first camp, what is the evidence in terms of the NREM-sleep-first position? Until recently, the observation of a lack of REM sleep in early mammalian species, such as the echidna, was considered to be strong argument in support of this position, but this was undermined by the discovery of large amounts of REM sleep in the platypus. To add further difficulties, there is much controversy over the existence or otherwise of NREM sleep in reptiles (Nicolau et al., 2000), studied largely because of the assumption that current versions retain many properties of earlier forms.

Notwithstanding these difficulties, we might ask, assuming NREM sleep is the first to be developed, what would be the adaptive advantage of REM sleep? Taylor et al. (2000) identify two possibilities. Firstly, a sentinel theory of the emergence of REM sleep suggests that during successive sleep cycles REM follows NREM to prevent a period of deep, unresponsive unconscious by increasing arousal, but to a lesser extent than wake. This period of increased arousal allows for the maintenance of

neuronal integrity and gives a boost to vital cardiac and respiratory systems that have otherwise slowed during NREM sleep. It also allows for ease of waking from a near-wake state, rather than the deeper NREM sleep. The difficulty for this position is that wake does occur from NREM sleep, with few ill effects, and is known to occur in hibernating species that spend long periods of time in NREM sleep. There is also the problem of a lack of thermoregulation during REM sleep, which intuitively does not fit well with a view that REM is a period of preparedness for wake. A second view, known as the dynamic stabilization theory, is more relevant for current theories of memory processing and REM sleep, and emphasizes the role of REM in the stimulation of neuronal synapses that might otherwise decay or be lost. These processes are further supported by the lack of muscle tone and effective paralysis of muscle activity, which might otherwise interfere with the maintenance of motor and sensorimotor circuitry by placing additional demands on these processes during sleep. The role of sleep in the maintenance of memory is intriguing and will be returned to later. For now, it seems that many researchers have decided to adopt the middle ground and accept that REM sleep is at least as old as NREM sleep, both emerging in response to a need to develop an alternative state to that of continuous wake.

Do all animals sleep?

If we look to the current similarities and differences across the animal kingdom, we can reflect on the variations between and within species and the relative importance of environment, lifestyle, and physiological influences on sleep behaviors, including the presence or absence of NREM and REM sleep, the role of the sleep cycle length, sleep duration, and placement. Siegel (2008) provides an extensive overview of studies to date, pointing out that only a limited number of species within each category of animal type have been subject to repeated, objective study, using well-established and comparable sleep-monitoring criteria. In his view, these criteria do not generalize easily across species. Also, in many cases, animals are observed outside their normal environments, suggesting that we have at best insight into how animals sleep within the artificial constraints of captivity. With this in mind, Siegel (2008) maintains that the observed variation in sleep between species can provide valuable clues to the functions of sleep.

There is the common sense assumption that sleep is vital and so essential to all species, and that without sleep death would follow. However, Siegel (2008) notes that some animals never seem to sleep, some go without sleep for long periods without apparent harm, and while rats die following extended experimentally induced sleep deprivation, this is not the case for all species, or following all experimental protocols. As for the suggestion that both NREM and REM sleep perform separate and essential functions, it is also noted that some marine animals do not have REM sleep, and it remains debatable whether reptiles, fish, and insects have REM sleep. In effect, Siegel (2008) argues, many of the common sense assumptions we hold for sleep are unsupportable in the light of what we know about animal sleep.

We often take for granted the assumption that sleep serves some restorative function, but, in terms of energy efficiency, REM sleep is at least as costly as wake (Horne, 2006; Siegel, 2008). The NREM rebound following sleep abstention, widely regarded as strong evidence in support of a homeostatic, restorative role for sleep, is not found in migratory birds following long periods of sleepless activity, and has yet to be found in migratory animals, or those showing large seasonal variations in activity prompted by food availability or reproductive behaviors. While all studies of mammals, mainly derived from zoo studies, show REM sleep in these animals, the greatest amount in any 24-hour period is unexpectedly found in the platypus (see above).

From what we know of fish, amphibians, or insects, Siegel (2008) concludes that there is no consistent evidence of a homeostatic role for sleep in these species, or evidence of REM sleep, as is the case for REM sleep in reptiles. In marine animals we have a number of interesting examples of adaptive sleep patterns. For example, during periods on land the fur seal exhibits cycling NREM and REM sleep in both hemispheres, but during extended periods in water (over weeks), a unique pattern of unihemispheric sleep is found. That is, sleep occurs in one hemisphere of the brain, coinciding with closing of the contralateral eye and inactivity of the contralateral flipper. The seal continues to receive incoming visual stimulus from the remaining open eye and to swim with the single flipper. In a similar fashion, dolphins are also found to show unilateral hemispheric sleep, but without the corresponding asymmetry in motor activity.

Following delivery in the dolphin and killer whale, newborn infant and mother swim continuously for 4–6 weeks without sleep. During a period of acute vulnerability, this is believed to be an example of the

dispensability of sleep in the face of pressing danger. So, according to Siegel (2008), sleep is not a universal process "with the same underlying vital function in all species," p. 212, or even, it would seem, within the same species across the life span.

If risk of predation following the birth of live young in dolphins and killer whales has such a marked effect on their normal pattern of sleep behaviors, we might assume that vulnerability of this type would influence a preference for sleep behaviors in other species. Capellini et al. (2008) asked whether a shorter NREM to REM sleep cycle length was related to risk of predation, proposing that a reduced cycle would allow greater vigilance for prey animals because of increased arousability at the end of each REM period. Along the same lines, it was also proposed that those animals with a high risk of being eaten might adopt a polyphasic sleep style across the 24-hour period, rather than a single episode of consolidated sleep (monophasic style). Contrary to these expectations, data from a total of 56 mammalian species—independently rated in terms of their risk of predation, sleep location, and number of episodes within a 24-hour period—failed to confirm correlations between risk of predation and sleep cycle length, nor did predation risk predict the adoption of a monophasic as opposed to polyphasic sleep style. Instead, polyphasic sleep was found in animals small in size with short sleep cycles. Despite this, these animals slept more in total across the 24-hour period than larger mammals with a monophasic pattern of sleep. These authors concluded that this reflects the metabolic constraints of small animals, with limited digestive capacity and the need to feed in small amounts at regular intervals. In addition, it was suggested that their extended total sleep time could be due to the increased amount of time in what is described as "transitional sleep," i.e., the lighter stages of NREM sleep, because of the number of sleep episodes in total. It is implied that these stages are of less restorative value than deeper NREM sleep and in that sense the shift toward monophasic sleep in large mammals, including humans, has considerable adaptive value by consolidating sleep in a single extended period, thereby reducing time spent in transitional sleep.

Interestingly, when Wehr et al. (1993) looked at extending sleep-time availability in humans (by eliminating external distraction and alternative stimulation throughout 14-hour nights in solitary darkness), sleep is seen to revert to a polyphasic pattern, with increased stage 1, 2, and REM sleep, increased wake between sleep episodes, increased total sleep time, and little consequence in terms of subjective or cognitive outcome measures. Humans are not the only animals to show increased sleep when there is very little else to do; baboons (Bert et al., 1975), cows, and ponies (Ruckebusche, 1976) also sleep longer when studied in captivity compared with their free-roaming state.

Given the diversity of sleep behaviors across species, and the apparent ability within species to adjust timing and duration of sleep in response to external factors, it is now useful to ask how the theoretical ideas of Kavanau (2002, 2004, 2005, 2006) on the evolutionary development of sleep and sleep function fit with this huge degree of variation. Kavanau (2002, 2004) argues that sleep evolved primarily to handle memory processing, and that for prehistoric animals, since requirements for complex memory processes were minimal if at all, there was no need for sleep. Coincident with the need for increased memory capacity came the development and reliance on more complex forms of visual acquisition apparatus and visual processing mechanisms. The first stage in this long process toward the development of the modern sleep state is considered to be the shift from a state of continuous active wake in support of a simple lifestyle of largely reflexive behaviors of predation, evasion, and reproduction toward alternating periods of active to restful wake. The requirement for a period of restful wake, characterized by a slowing of the EEG frequency, most likely the first move toward the slow waves currently found in the sleep of reptiles and NREM sleep of birds and mammals, was necessitated by a requirement for long-term storage of basic memories. Given only limited available processing capacity, arguably fully engaged with incoming sensory information and motor response during active wake, the need for some period of disengagement emerged. The key to this, according to Kavanau (2005, 2006), is the development of detailed focal vision (DVF), allowing the extraction, processing, and storage of more information from the visual field. During periods of active wake, animals are no longer solely preoccupied with automatic reflexive behaviors, but show, for the first time, the capacity to learn, based on the accumulation of experiential memories.

Restful wake, eventually to become primitive sleep and finally NREM and REM sleep, allowed some resolution of the conflict between the need to deal with the immediate incoming sensory information and the need to secure time for learning and memory processes within the constraints of a very basic nervous system. The advantage of sleep in

terms of its substantial survival value in providing an efficient and effective use of limited neural structures would ensure positive selection. So how does this explain the huge variation in sleep patterns across current species and, perhaps more strikingly, the apparent success of animals without sleep?

Fish that do not sleep, according to Kavanau (2002, 2004, 2008), including schooling fish, tuna, and some sharks, live in environmentally impoverished, predictable conditions and follow a lifestyle of largely automatic behaviors based on inherited or intuitive hard-wired reflexes with little need for huge stores of learned memories. So, in spite of having good visual function, there is little requirement for sleep due to their low memory needs, as processing conflict does not arise. In contrast, fish and other marine species with different environmental challenges sleep for the reasons outlined above. Similarly, some animals without vision, such as the genetically blind cave bat, do not sleep, presumably because they do not have the heavy processing demands of relatively huge amounts of visual input found in most other species, or even in a closely related species of bat that, under different environmental conditions, retained their vision (Kavanau, 2006).

An important aspect of Kavanau's argument (2005, 2006) proposes a separation between the functions of NREM and REM sleep, again emphasizing their role in memory processes. This division is used to explain the lack of one sleep state or the other both between and within species. NREM sleep is described as necessary for the reinforcement of uncoordinated memory, whereas REM sleep deals with coordinated memory reinforcement, principally the reinforcement of motor circuitry, hence the need for loss of muscle tone, without which motor circuits would be engaged in the unnecessary distraction of processing movement during this sleep state. The effect of this unwanted muscle activity would be to reduce overall efficiency of the memory process, one of the main factors in necessitating the need for sleep in the first place.

So why do some animals manage perfectly well without REM sleep? It is argued that the lack of evidence for REM sleep in dolphins, porpoise, and white whales is due to the fact that they are in constant motion and so there is no need for reinforcement of visual and motor circuits. As noted, they have a unihemispheric form of NREM sleep and, apparently, excellent memories, so the need for REM sleep is low. The same is argued to be true of some birds thought to have unihemispheric NREM sleep during flight. Consistent with this point is the finding that birds engaged in more flight time have less REM sleep, whereas flightless birds, such as penguins, have more REM sleep.

The extent to which environmental factors govern differences in sleep patterns within the same species was recently illustrated by Kavanau (2006) when discussing the data from a telemetric study of jellyfish (cubomedusae jellyfish—*C. flickeri*) swimming freely in their natural environment and shown to sleep for up to 15 out of 24 hours. Consistent with previous arguments, the need for excessive amounts of sleep is believed to be due to the fact that this type of jellyfish has multiple pairs of eyes of a similar complex design to vertebrate eyes and that their predatory eating behaviors rely on the surveillance of a challenging visual field and an extremely fast motor response. Sleep is seen to be an essential response to the processing demands of this highly sophisticated visual apparatus on a comparatively simple nervous system. However, when observed in captivity, with ready access to essential food supplies, this same jellyfish has a greatly reduced need for sleep.

This is claimed to be the only known example where the need for sleep within a species is determined solely by their environmental conditions (Kavanau, 2006), yet very few species are studied in contrasting environments. When they are, as with the limited zoo versus free-range animal studies, we see a shift toward more sleep (not less) in certain mammals (Bert et al., 1975; Ruckebusche, 1976). We might even include humans in this category who, under conditions of very little stimulation or alternative to sleep, are often observed to extend their sleep beyond normal parameters (Wehr et al., 1993; Roehrs et al., 1989, 1994; Harrison & Horne, 1996). We also see something of this in sharks, where one type might inhabit an environment requiring low processing needs and therefore no sleep (open seas) and another might live more in-shore, having a greater need for long-term memory storage of local reference points and complex feeding styles, so they do sleep (Kavanau, 2005).

To summarize this position

1. Kavanau (2005, 2006) emphasizes the importance of the relationship between sleep and visual processes. Firstly, it is pointed out that all sleeping animals aim to reduce visual input by closing their eyes and choosing a suitable location with minimal visual distraction (while also benefiting from the earlier adaptation from

transparent to opaque eyelids). Furthermore, relative to other senses, vision requires a huge amount of processing capacity, even without directed attention. In some birds and marine animals, sleep is instantaneous for half of the brain on closing of the eyes. Secondly, he makes the case that only animals with the capacity for detailed focal vision (including vertebrates and invertebrates) sleep. Animals with no vision do not sleep, presumably because there is no conflict in processing demands between huge amounts of visual incoming data and memory, e.g., genetically blind cave fish. On the other hand, the absence of sleep in animals with detailed focal vision (see above) can sometimes be explained in terms of their lifestyle, i.e., lack of behaviorally challenging environment.

2. Theories relating to the evolutionary development of sleep continue to be highly influential in guiding current research into the specifics of the relationship between sleep and memory. Both NREM and REM sleep are thought to be periods associated with the enhancement of memories, although there are many difficulties in modeling "memory" as a cognitive process, with much resulting inconsistency in this literature. Some species have no need for REM sleep, and others, such as humans, manage well without REM sleep for long periods of time. It is argued that this is due to the highly adaptive nature of brain processes that allow the more primitive memory functions of NREM sleep to effectively, if less efficiently, complete the task of memory processing. This might explain the lack of memory deficit despite long-term use of REM-suppressant drugs, such as MAOI inhibitors or antidepressant tricyclics, or the preservation of memory during extraordinarily lengthy periods of sleep (encephalitis lethargica) (Kavanau, 2005). Note, however, that some researchers have taken this argument a step further by suggesting that these processes might also be covered perfectly adequately during the waking state, thereby negating the role of sleep as essential in this regard (Vertes, 2005; Rial et al., 2007; Vertes & Siegel, 2005); more below. It is now time to look at the sleep-dependent memory hypothesis in further detail.

Current focus on sleep and memory

Since the mid-1990s, we have experienced a renewed interest in the field of sleep and memory research, which is in part due to technological advances enabling the study of neuroanatomical features of brain activation during sleep (Maquet, 2000; Taber et al., 2006) and following sleep deprivation (Drummond et al., 2000, 2001; Thomas et al., 2000), but also coincident with the appealing evidence from evolutionary and comparative studies outlined above. The extent to which sleep is implicated in memory function is so compelling for some researchers that it has been argued that, in humans, some aspects of visual memory can occur only during sleep (Gais et al., 2000; Stickgold et al., 2000). However, despite the vast number of study hours devoted to this subject in recent years, this field is marked by inconsistencies and failure to provide conclusive evidence of the precise nature of the link between sleep and memory. It appears that there is more agreement on the role of sleep in reinforcing procedural memories (the acquisition of skills, tasks, and expertise) and less with declarative memory (facts, knowledge, and episodic details of an event) (Stickgold et al., 2000).

Walker (2005) provides a theoretical framework with which to understand much of this inconsistency by differentiating between three stages of memory: an acquisition process that occurs mainly (and most effectively) in wake but can be shown during sleep, a stabilization process that takes place following acquisition and is reliant on the passage of time rather than sleep, and an enhancement process that is dependent on sleep. Following acquisition of a procedural skill, a memory trace is believed to be fragile, requiring further reinforcement. This reinforcement is understood to take place over a period of between 15 minutes to 6 hours following skill acquisition. Between skill acquisition and stabilization that memory is vulnerable, and further consolidation is not guaranteed. An example of how this works is offered by Muelbacher et al. (2002) in which, following acquisition of a motor skills task, participants showed expected improvement in task performance at the end of a training session. This was persistent on retest after a 15-minute interval. However, interference for one group using repetitive transcranial magnetic stimulation (rTMS) during the 15-minute interval resulted in a return to pre-training levels of performance. Furthermore, when an additional group of participants underwent the same interference technique, but this time at 6 hours following the end of the training session, performance was found to remain at post-training levels. It is assumed, therefore, that the stabilization process occurs sometime between 15 minutes and

6 hours, and that certainly by the 6-hour point that memory is no longer vulnerable to the distraction of an interference process. Prior to stabilization, the memory can be lost. In no condition did performance actually improve from post-training levels. Further evidence suggests that memory for visual and motor procedural skills gained during training can persist throughout up to 12 hours of wake (Walker et al., 2002, 2003).

Perhaps more remarkably, there is growing evidence to show improvement in performance without further training, following a night of normal sleep (Karni et al., 1994; Brashers-Krug et al., 1996; Shadmehr & Brashers-Krug, 1997). To counter criticism of a time-dependent rather than sleep-dependent mechanism involved in this improvement, Walker et al. (2002, 2003), again using a motor task, trained participants at either 10 a.m. or 10 p.m. As expected, there was an effect of training with a 60% improvement in performance for both groups at the end of the training session. Both groups were tested again following an intervening 12-hour period. For the 10 a.m. morning training group this intervening period was made up entirely of wake. Performance indicated that stabilization but not enhancement had taken place, with levels similar to that of the end of the training period. In contrast, participants trained at 10 p.m. showed improvement in performance (20% speed, 39% accuracy) at 12 hours post-training, following an intervening night of sleep. At 24 hours post-training, the morning group, having now had the opportunity to sleep, showed similar improvements to the night-training group at the 12-hour post-training trials. However, the night-training group showed no further benefit at the 24-hour post-training trials. These authors conclude that the additional learning (delayed in the morning group despite the equivalent interval between tests) is facilitated by the opportunity for sleep, and not simply the passage of time.

Will any sleep state suffice to facilitate enhancement? Walker et al. (2002) found a correlation between magnitude of improvement and time spent in stage 2 NREM sleep as a proportion of overall sleep time. But this is not consistent with other studies, and it is suggested that task complexity and sensory demands are likely to account for these inconsistencies. Further evidence of performance improvement following sleep covers visual discrimination tasks (Karni et al., 1994), visual motor skills (Maquet et al., 2003), and auditory tasks (Atienza et al., 2002, 2003).

There are some difficulties with the design of the Walker (2002) study, in particular with the introduction of time of day of training and testing as a potential confound (Siegel, 2005). Coenen (2005) also argues that the Walker (2002) study does not provide evidence of an active role for sleep in the enhancement of memory, but that the effectiveness of sleep may be in providing a period of time free from the competing distraction of interference. In that sense, sleep is considered to be a passive process, favorable, but not essential, to the enhancement of memory.

Having to some extent predicted this argument, Walker (2002, 2003) studied a third group of participants who were this time requested to wear mittens between 10 a.m. training and 12-hour post-training trials. This simple measure was intended to inhibit the use of motor skills between trials, as might happen if the main role of sleep was to eliminate or greatly reduce the demand on related motor circuitry. If, in this scenario, sleep simply dampens motor activity to allow enhancement, one might expect the mittens to be an effective alternative in achieving this end, even during wake. This was not found to be the case, as the absence of hand movements during wake did not lead to further enhancement of performance. However, following a night of sleep, this group showed improvement at the 24-hour post-training trial.

Critics of this view of sleep-dependent memory processes point to the many studies that have failed to establish this link between an essential need for sleep prior to enhancement, including Atienza et al. (2005), in which performance on an auditory discrimination task was enhanced despite 48 hours of sleep deprivation, and Doyen et al. (2005), who found that the passage of time was sufficient for improvement on a motor task. It has also been argued that while REM deprivation or suppression does not lead to memory impairment, nor do learning challenges increase the need for REM sleep. We might think back to the argument put forward by Kavanau (2005) in which he advocates that NREM memory processes, while more primitive and inefficient, take over in the absence of REM. Does this explain inconsistencies in attributing enhancement processes to sleep states (Walker, 2005), and is there sufficient evidence to show an essential role for sleep in memory function?

Piggott and Perry (2005) point out further obvious inconsistencies with the sleep-dependent memory process position, this time from the clinical field and including studies that show that insomnia is

not consistently linked with poor memory, that pharmacologically increased total sleep time does not lead to improved memory, that the sleep disturbances of Parkinson's disease are not related to memory dysfunction, and that normal age-related reduction in total sleep times is not correlated with memory deficit.

Vertes (2005) is also critical of sleep-dependent memory process on the strength of current evidence arguing instead that "at best consolidation based enhancement [of memory] is a slow, time-dependent process of consolidation that begins with task acquisition in waking and can under some circumstances extend to sleep" (p. 86). We are again reminded that REM sleep does not increase following a heavy learning challenge, and that memory problems do not follow from the artificial suppression of REM sleep. While we assume that an intervening night of sleep is responsible for improvements in procedural skills in an experimental setting, improvements without further practice will occur over time anyway, suggesting that some aspect of consolidation is achievable during wake. Interference and distraction are important issues in the formation of memory, but there is insufficient evidence at this time to assume that the role of sleep is anything other than to minimize their effect and that, given favorable conditions, this could be achieved equally well during restful wake (Vertes, 2005; Vertes & Siegel, 2005).

Is all sleep essential?

Before moving on, it is perhaps important to point out that not all sleep researchers are currently absorbed by this debate and that, for some, the role of sleep and memory is largely overstated. Somewhat reminiscent of his earlier work on core and optional sleep, Horne (2006) has recently advised that ". . . our sleep alters as a night's sleep progresses, initially serving important purposes, changing to those of less benefit, and eventually to a sleep that is superfluous, luxurious and just pleasant to take" (p. 893). We can assume from this that as the latter stages of sleep comprise mainly REM and stages 1 and 2 NREM sleep, at least some part of a nightly NREM and REM quota is understood to have little essential function.

The role of the NREM rebound following sleep loss is believed to be compelling evidence in support of a restorative role for sleep (Borbely & Tonini, 1998). The need for sleep is a function of both homeostatic and circadian processes, increasing throughout the day largely independent of cognitive or physical activity. Time awake is the critical factor in terms of the NREM rebound, i.e., increased duration and intensity of NREM periods, usually in the first half of the night, in response to increased periods of wake. Increased intensity of slow-wave activity is predominant in the frontal regions of the brain and has been linked with deterioration in executive-type skills following sleep loss (Muzur et al., 2002). The reverse, reduced duration and intensity of delta activity in the first two cycles of sleep, has also been shown following reduced periods of wake time between sleep episodes (Harrison & Horne, 1996). However, contrary to expectations, and as has been described earlier, the NREM rebound is not universal across species. For rats and pigeons, a REM rebound is observed following sleep loss, whereas migratory birds or those experimentally deprived of sleep show no sign of rebound sleep (Siegel, 2008).

Short and long sleepers have comparable amounts of slow-wave sleep. Differences in sleep architecture lie in the amounts of REM and stages 1 and 2 NREM sleep (Borbely & Tonini, 1998), suggesting that they are better able to tolerate longer wake periods with few difficulties in terms of physiological or cognitive performance, while satisfying an essential need for sleep within a shorter sleep episode. Interestingly, there was some controversy, first voiced in the 1970s (Webb & Agnew, 1975; Carskadon & Dement, 1979), gathering momentum in the 1980s (Carskadon et al., 1986; Roehrs et al., 1989) peaking in the mid-1990s (Bonnet & Arand, 1995; Harrison & Horne, 1995; Roehrs et al, 1994), and continuing more recently (Balkin et al., 2008; Banks & Dinges, 2007; Klerman & Dijk, 2005; Van Dongen et al., 2003; Vgontzas et al., 2004), concerning the question of whether the general population of the Western world was getting enough sleep. The view that many individuals are chronically sleep deprived rested on the assumption that as humans could be encouraged to sleep more than their habitual amount, this extra sleep was probably necessary, with sole benefits in terms of relief from subsequent objectively defined sleepiness (although mainly during the combined influence of circadian "low points"). This debate is likely to continue for some time as researchers continue to question the relationship between sleep and daytime waking function.

In terms of more acute, total sleep loss, much research has focused on the specifics of cognitive deficits, whether it be to memory systems, attention, arousal, or more generalized performance. In recent