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Edited by Eric Nofzinger, Pierre Maquet and Michael J. Thorpy
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Section 1 Introduction

Chapter 1

The role of neuroimaging in sleep and sleep disorders

Eric Nofzinger

Introduction

This book, entitled *Neuroimaging of Sleep and Sleep Disorders*, is a timely collection describing state-of-the-art research related to imaging the brain, both structurally and functionally, in relation to the broad topic of sleep and its disorders. The work described represents the cumulative integrated knowledge to date from several key developments in science over the past six decades. First, since the 1950s, fueled by seminal findings in the explorations of the nature of sleep, basic science research has led to an incredibly rich understanding of the neural underpinnings of the global states of consciousness defined largely by the electroencephalogram (EEG), including waking, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. As a result of this research, sleep is no longer a mysterious state of being, impervious to scientific study, but now is understood to be a rich tapestry and integration of discrete behavioral states, each with well-defined interactions in neural circuitry. Second, at the human level, sleep has been shown to play a fundamental role in human behavior, involving interactions between homeostatic, circadian, and cognitive functions. Third, a clinical field of sleep medicine has evolved that has defined how sleep is disrupted in humans, leading to significant detrimental impacts on function, resulting in human suffering. Much of this pathology and its manifestations involves how the brain functions either normally or abnormally in clinically recognized sleep disorders such as the insomnias, sleep apnea, narcolepsy, and the parasomnias. Fourth, a field of cognitive neuroscience has fluorished in which the brain is now understood, at it's highest level of organization, to have regional brain specificity for particular behaviors and cognitive processes, such as motor behavior, sensory processing, thought, and emotion. Much of this new knowledge has come from brain imaging studies performed during waking. Fifth, there have been enormous technical developments in ways to "image" the human brain, at both the structural and functional levels, such as magnetic resonance imaging (MRI), positron emission tomography (PET) and functional MRI (fMRI), making possible the testing of hypotheses at a regional brain level in relation to human behavior, health, and pathology. This book represents the first major overview of the wisdom generated from these cumulative scientific developments towards the study of sleep and sleep disorders.

Basic sleep mechanisms and neuroimaging technology

Sleep is perhaps in a unique position for study via neuroimaging. Sleep is now understood to be a manifestation of the brain, and more specifically, the result of interactions in discrete neural networks that result in the global states of consciousness we recognize at the EEG level, those of waking, NREM, and REM sleep. Importantly, the study of sleep has brought to the forefront our understanding that brain function at a global level is not a static process, but rather evolves, in a rhythmical and highly regular manner across a 24-h cycle. In no other area of neuroimaging research has the temporal domain of brain function taken on such heightened significance. It is now understood that it is not only important to know "what" is being imaged, but "when," and that the object of study from a neuroimaging standpoint changes dramatically based on this temporal variable. Imaging brain function in waking will produce dramatically different results than imaging during sleep. Within sleep, brain activity will be globally and regionally different if studying NREM or REM sleep, or even within these larger states, if one is focusing on some discrete aspect of NREM sleep or REM sleep, such as slow waves or rapid eye movements. Even within waking, we now understand that brain function changes significantly across a normal day, from morning to evening, or with varying degrees of alertness or sleep deprivation.

The field of neuroimaging has had significant advances in the past four decades. The advent of computed tomography, or CT, allowed visualization of brain structure in a living human. CT scans provided clarity on bony structures primarily but had less ability to define internal brain structures. Limitations of CT scanning included exposure of an individual to ionizing radiation and limited ability to detect brain tissue differences. The development of MRI, or MR scanning, allowed for the detection of more subtle changes in brain tissues and did not involve exposure of the subject to radiation. Applications of structural imaging to sleep and sleep disorders, primarily using MR methods have defined brain structural changes that are related to pathophysiology or consequences of suffering from a specific sleep disorder.

Greater insights into the mechanisms and consequences of sleep and sleep disorders have been achieved through advances

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More information

Table 1.1. Functional neuroimaging tools for sleep. This table outlines various functional neuroimaging modalities and their benefits/limitations for the study of brain processes during sleep.

	MEG tomography	fMRI	$H_2{}^{15}O$ PET	^{18}F-FDG PET	^{99m}Tc-ECD SPECT	Receptor imaging
Measure	Electrical events	Blood flow	Blood flow	Metabolism	Flow/ Metabolism	5-HT, DA, ACh, GABA
Spatial resolution	10 mm	< cm	cm	cm	cm	cm
Temporal resolution	Milliseconds	Seconds	Min	10–20 min	Min	20–90 min
Sleep in scanner?	Yes	Yes	Yes	No	No	Waking
Other	Difficult in sleep Availability, expense	Noise, technically difficult in sleep	Repeated measures possible	Long half-life limits repeated measures	Repeatable in single night	Expensive, labor intensive

FDG = fluorodeoxyglucose; ECD = ethyl cysteine dimer; 5-HT = 5-hydroxytryptamine (serotonin); DA = dopamine; ACh = acetylcholine; GABA = gamma-aminobutyric acid.

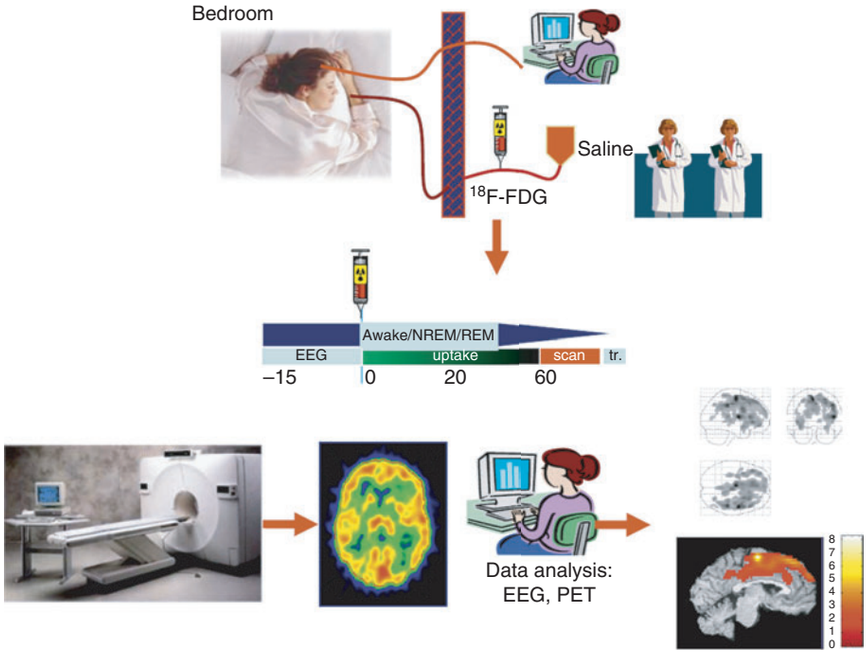

Figure 1.1 This figure depicts the application of the ^{18}F-FDG PET method for studying regional brain function during sleep. In this method (top of figure), the subject sleeps in a bedroom environment while recording equipment and technical staff for monitoring sleep and making radioisotope injections remain outside the sleeping environment in an adjacent room. The middle of the panel outlines the timing of injection and radioisotope uptake timing in relation to the temporal sequence of distinct behavioral states of waking, NREM or REM sleep. The bottom panel shows the PET scanning environment and data and image management that provide visualization of regional brain function during sleep.

in brain imaging methods that describe various aspects of neural "function." These are collectively referred to as functional neuroimaging. These include techniques such as PET, fMRI, single-photon emission computed tomography (SPECT), transcranial sonography, magnetoencephalography (MEG), low-resolution brain electromagnetic tomography (LORETA), and combined methods such as combined EEG and fMRI (Table 1.1, Figure 1.1). In each of these methods, there are assumptions between what the brain is doing (e.g., neuronal activity) and the measured process (e.g., changes in blood flow or metabolism). In most cases, these tools have been developed for the study of waking brain function and the assumptions underlying the measurements apply to waking brain activity. It is generally assumed, though probably not as rigorously validated as one might like, that the assumptions between what the brain is doing and the measurement are similar across brain states of waking, NREM, and REM sleep. Additional research is needed in this area. Still, the applications of these methods for the study of sleep and its disorders, make up the bulk of the information related to neuroimaging of sleep and sleep disorders that we now know.

Neuroimaging of wakefulness and sleep

The earliest applications of neuroimaging to the study of sleep and its disorders were those of functional neuroimaging methods to study the global brain states of waking, NREM, and REM sleep (Figure 1.2). Prior to the application of these methods, knowledge of these gross behavioral states and their mechanisms

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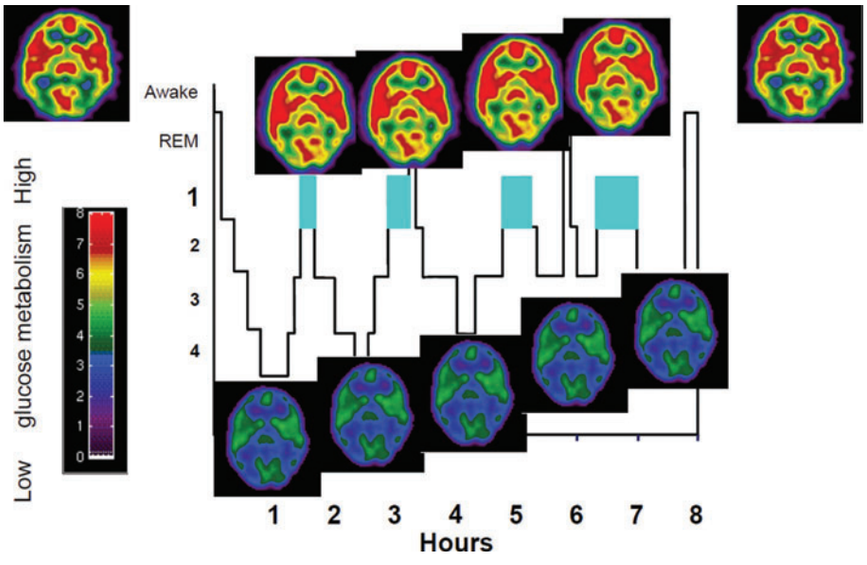

Figure 1.2 This figure depicts global changes in brain activity across the sleep/wake cycle. Global brain activity is highest in waking before and after sleep. Global brain activity is lowest in a 24-h cycle early in the night during slow wave sleep. In REM sleep, global brain activity, in connection with cortical activation at the EEG level, approximates, but does not reach, that of wakefulness. As viewed here, global brain function maintains dramatic cyclical variations in a regular manner across the sleep/wake cycle.

came largely from preclinical work. Basic science methods utilized existing neuroscience tools for assessing electrophysiology and the cellular and molecular mechanisms of sleep. The general understanding was that sleep/wake function could be defined by discrete global electrophysiological signals that differentiated various states of neural processing such as waking, NREM and REM sleep. Early brain imaging work during sleep, therefore, was somewhat exploratory and descriptive, defining large-scale changes in regional brain activity across these states of consciousness. As this had never been done before, the novelty of these early findings revolutionized our general understanding of human sleep in terms of the coordinated neural networks involved. While preclinical work had largely focused on the switches defining the regulation of sleep at a brainstem and hypothalamic level, the human sleep neuroimaging findings drew attention to the involvement or participation of higher levels of the central nervous system that likely play fundamental roles in the overall function of sleep. More recent analyses have focused on higher resolution temporal events such as phasic and non-phasic aspects of each individual state and validating neural changes in the brain as predicted from the preclinical sciences.

Neuroimaging and sleep loss and circadian misalignment

Aside from knowledge of the neural underpinnings of sleep derived from the preclinical basic science literature, there existed a long line of behavioral human sleep research that had defined the relationships between human sleep loss and performance. Extensive evidence defined both homeostatic and circadian influences on sleep and disruptions in either of these domains even in an otherwise healthy individual lead to predictable changes in alertness, cognition, and performance.

Extensive scientific progress in the area of chronobiology has also been made over the past quarter century, spawning a large academic and clinical discipline. The scientific investigation and understanding of these rhythms dramatically accelerated with the discovery of the suprachiasmatic nuclei (SCN) as the site of the biological clock [1, 2]. Extensive preclinical work has advanced our understanding of the molecular and genetic basis of circadian rhythms [3–10]. Although both photic and non-photic stimuli have been known to influence circadian rhythmicity in animals and man, light is considered to be the dominant synchronizing input [11].

Extensive applications of brain imaging have been made, largely functional neuroimaging, to help clarify the changes in regional brain function that result from perturbations in either homeostatic or circadian processes, and also have clarified the relationship between these brain changes and the behavioral consequences of these disruptions.

Sleep and memory

While disruptions in sleep were well recognized to result in changes in human behavior during waking function as measured by various performance and alertness measures, an extensive line of research was beginning to look at a potential role for sleep in terms of brain plasticity, or the capacity of the nervous system to change its structure, and its function, over a lifetime, in reaction to environmental diversity. Brain plasticity could include concepts such as synaptic plasticity, neurogenesis, and functional compensatory plasticity, concepts that had been evolving in the basic and cognitive neurosciences but previously had not been applied to the study of sleep. This area of research developed some of the most exciting hypotheses that sleep contributes importantly to processes of memory and brain plasticity. Over the past few decades, a large body of work, spanning most of the neurosciences, has provided a substantive body of evidence supporting this role of sleep in what is now known as sleep-dependent memory processing. This includes memory encoding, memory consolidation, brain plasticity, and memory reconsolidation. Extensive evidence from functional brain imaging studies support this emerging model of one of the critical functions of sleep.

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Neuroimaging of sleep disorders

While disruptions in sleep are not new to humanity, significant attention to these disturbances as a public health concern worthy of medical attention and treatment has only emerged in the past four to five decades. Sleep medicine has only recently been recognized as a specialty of medicine. Its development is based on an increasing amount of knowledge concerning the physiology of sleep, circadian biology, and the pathophysiology of sleep disorders. Scientific progress combined with an increasing recognition that disorders of sleep are highly prevalent in society has led physicians to acquire knowledge necessary for the diagnosis and treatment of disorders of sleep. Centers focused on the evaluation and management of sleep disorders have developed only within the past quarter-century.

Sleep neuroimaging of sleep disorders has paralleled the development of this evolving field of medicine. Within the field of sleep disorders medicine, the polysomnographic evaluation of sleep has been the mainstay of the evaluation of sleep disruption and the effects of interventions. This is largely related to early work identifying discrete sleep stages and the evolution of sleep across a night based on electrophysiological markers of the global brain states of waking, NREM and REM sleep. Brain imaging methods can provide a needed additional breadth of knowledge in a new domain to the understanding of the neurobiology of discrete sleep disorders. Indeed, in some cases, such as primary insomnia, brain imaging studies have been shown to be more sensitive to defining pathology than traditional sleep EEG. The field of sleep neuroimaging holds promise for future use in clinical sleep medicine not only as a research tool to understand pathophysiology, but clinically in terms of diagnosis and prediction and monitoring of treatment effects. Future clinical applications will depend on advances in our understanding of individual disorders as well as technical refinements in imaging methods that should make them cost-effective and widely available for future use in sleep medicine.

Insomnia and circadian rhythm disorders

Insomnia is the most prevalent of all sleep problems. Insomnia is the subjective complaint of difficulty falling asleep, difficulty staying asleep, poor quality sleep, or inadequate sleep duration despite having an adequate opportunity for sleep. Importantly, EEG sleep alterations in insomnia are not always found in individuals with subjective complaints of insomnia. The leading neurobiological model of insomnia is that of hyperarousal. For instance, individuals with insomnia have been shown to have elevated temperature and muscle tone at sleep onset, elevated heart rate and elevated sympathovagal tone in heart rate variability, and positive correlations between wake time after sleep onset and urinary norepinephrine and dopamine metabolites [12–15]. Studies of whole-body metabolic rate, assessed by oxygen consumption, show elevated rates for individuals with insomnia compared to healthy controls, a difference that persists 24 h per day [16]. The hyperarousal of insomnia is supported by higher rates of self-reported ruminations and intrusive thoughts among insomniacs.

Perhaps among all the sleep disorders, brain imaging studies have been most helpful in elucidating the neural substrates of hyperarousal. An emerging body of evidence exists where there has been identification of regional brain alterations despite the relative absence of EEG sleep signs of the disorder. These findings hold promise that the use of brain imaging in this disorder can considerably advance our understanding of the disorder and lead to new mechanisms for treatment in a manner previously unattainable through traditional EEG sleep assessments.

Neuroimaging of central nervous system hypersomnias

Narcolepsy consists clinically of excessive daytime sleepiness in combination with cataplexy, a loss of muscle tone in response to laughter and other emotional stimuli. Some patients also experience paralysis or hallucinations at sleep onset and on awakening. A major breakthrough in our understanding of the neurobiology of this disorder occurred in the past several decades. In 1998, two peptides were identified in the hypothalamus and named hypocretin (Hcrt)-1 and Hcrt-2 [17], names reflecting their hypothalamic origin and homology to secretin. Almost simultaneously, another group of investigators independently identified the same peptides, which they named orexin-A and orexin-B, based on their appetite-stimulating effect [18]. These molecules arise from a precursor, preprohypocretin, synthesized by a small number of cells in the posterior and lateral hypothalamus, especially the perifornical area. They project to a diverse set of targets in the brain and spinal cord, especially the monoaminergic and cholinergic fields of the brainstem tegmentum comprising the ascending reticular activating system (ARAS) [19, 20].

Following preclinical findings regarding the role of the Hcrt system in narcolepsy, studies of narcoleptic patients revealed low or undetectable Hcrt-1 in the cerebrospinal fluid (CSF) of most (87%) patients with cataplexy and in some patients without cataplexy (14%) [21]. Clinical manifestations of the disease, such as cataplexy, appear to reflect a lack of Hcrt-mediated synaptic excitation of serotonergic and noradrenergic pathways normally responsible for REM sleep inhibition. The sleepiness of narcolepsy more likely reflects lack of Hcrt's excitatory influences upon histaminergic, dopaminergic, and cholinergic components of the ARAS, which normally function to promote thalamocortical arousal.

Brain imaging studies have been utilized in narcolepsy and the hypersomnias. Importantly, both structural and functional neuroimaging methods have been applied to the study of this disorder. While results to date have not been as clear as some of the preclinical genetic work in this disorder, this area remains fertile ground for future studies in understanding the neurobiology and behavioral manifestations of the disorder.

Neuroimaging of sleep-related breathing disorders

In 1965, Gastaut *et al.* documented repetitive episodes of upper-airway obstruction terminated by brief arousals that in turn

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fragmented nocturnal sleep in patients who subsequently would be referred to as having obstructive sleep apnea (OSA) [22]. It was postulated that sleep fragmentation was responsible for the excessive daytime somnolence observed in these patients. Subsequently, it has been determined that reductions in tidal volume (hypopneas) as well as increases in upper-airways resistance also produce sleep fragmentation and daytime sleepiness.

This major new concept in medical science stimulated considerable research in the area of sleep and breathing. An early discovery by Remmers *et al.* documented the relationship between intraluminal airway pressure and electromyogram (EMG) activity of the genioglossus muscle in the pathophysiology of upper-airway collapse in the pharyngeal segment of the airway, and tracheostomy was recognized as an effective treatment [23]. Later, Sullivan *et al.* demonstrated that the application of continuous positive airway pressure (CPAP) via the nose would prevent upper-airway collapse, normalize nocturnal sleep, and alleviate daytime hypersomnolence [24]. This latter discovery revolutionized the treatment of OSA and has resulted in the use of nasal CPAP as the most commonly used treatment of this condition.

This high prevalence in the population combined with evidence suggesting adverse cardiovascular consequences led to studies investigating these important relationships. Resulting publications established a clear association between sleep-disordered breathing and the development of hypertension, along with an increased prevalence of coronary heart disease, heart failure, and stroke at levels of an apnea-hypopnea index equal to or greater than five per hour [25–27]. Much of the growth of the field of sleep medicine can subsequently be attributed to the need for diagnostic and treatment centers to address the large population of individuals suffering from this disorder.

Brain imaging studies have rapidly evolved in the area of OSA syndrome. Brain MR studies have been performed to describe volumetric changes in discrete regions of the brain that may play a role in the pathogenesis of the disorder or as a manifestation of having OSA. MR studies have also been used extensively to define the anatomical abnormalities in the upper airways of patients with these disorders that contribute to the obstructed breathing. Functional brain imaging studies have demonstrated mechanisms related to ventilatory control in the central nervous system, the adverse consequences of sleep apnea on neural function, as well as their reversal with treatment with CPAP.

Neuroimaging of parasomnias

Parasomnias collectively refer to disorders of abnormal behavior during sleep. One of the most striking parasomnias is REM sleep behavior disorder (RBD), in which skeletal muscle remains active during dreaming, resulting in vocalization and sometimes violent activity of the arms and legs. The physiology underlying normal REM sleep atonia has been elucidated at the preclinical level and involves alterations in a descending motor inhibitory pathway from cells of the pedunculopontine nuclei that lie in close proximity to the primary REM sleep generator in the dorsal pons [28].

In humans, much interest has been generated because of the relationship between RBD and certain specific neurodegenerative disorders [29–35]. At least 50% of patients in large studies carry diagnoses of Parkinson's disease, multiple system atrophy, or dementia. There is also retrospective and prospective evidence that RBD may sometimes be the first manifestation of one of these neurological disorders, and thus at least some patients with apparently idiopathic RBD may with time evolve to develop a neurodegenerative disease. Most of the brain imaging studies in the area of parasomnias have explored these types of relationships through both structural and functional neuroimaging studies as well as in informative case studies.

Neuroimaging of other sleep-related neurological disorders

Much brain imaging work has been conducted in the area of restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS). RLS may be one of the most common sleep-related disorders, with a prevalence as high as 10% [36]. Patients complain of severe discomfort in their legs while sitting or lying in bed, associated with an uncontrollable desire to move to obtain relief. Almost 90% of patients experience regular jerks of their legs while asleep, known as PLMS.

A range of studies using different methodologies has produced striking insights into the pathogenesis of the disorder. Pharmacological studies have indicated that levodopa and dopamine-receptor agonists are effective therapies for RLS, indicating that the disorder is associated with a decrease in dopaminergic function in the brain. Brain imaging studies in these disorders, then, have focused on the dopaminergic system via PET ligands in the dopamine system and functional brain imaging studies have focused on regions of the brain involved in motor behavior [37–39].

Another interesting development in understanding the pathogenesis of RLS is related to iron metabolism. Studies have revealed that RLS severity correlates with serum ferritin concentrations below 45 to 50 mg/l, values usually considered in the normal range [40, 41]. Low ferritin concentration in the CSF has been demonstrated in RLS patients with normal serum ferritin concentrations compared to controls, suggesting that low iron stores in the brain may be associated with RLS [42]. Functional imaging studies have therefore focused on assessing brain iron in regions of the brain related to motor behavior.

Neuroimaging of medication effects

Management of several sleep disorders is improved with pharmacological interventions. Examples include periodic limb movement disorders, narcolepsy, and the insomnias. Functional neuroimaging studies may provide important information regarding pharmacotherapy in several realms: drug development, assessment of mechanism of action of therapeutic compounds and assessment of treatment response/non-response to pharmacological agents.

A variety of compounds have been discovered with mechanisms of actions that may affect sleep/wake regulation. Testing in preclinical models suggest that these compounds may have novel mechanisms of action; however, the degree to which these mechanisms will translate into a clinical application are often

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unknown. Functional neuroimaging studies may identify the degree to which these compounds have beneficial mechanisms of action on brain structures that are known to regulate behavioral states in humans. One way of achieving this goal is to administer the compound to human subjects, then assess a functional neuroanatomical response to the compound within sleep in humans, such as a regional blood flow or metabolism. Further, these studies may help to determine the optimum dose of the compound in humans that maximizes beneficial effects of the compound, yet does not lead to adverse effects. The use of receptor ligands may clarify whether one compound has a unique mechanism of action on a specific receptor subtype that may not be shared by other compounds in its class and may therefore hold a therapeutic advantage over other agents. Finally, once a compound has been identified and shown to have effects in the central nervous system in humans, functional neuroimaging studies can then be used to determine the degree to which the compound reverses distinct alterations in neural function in a clinical population.

Future directions

The field of brain imaging in relation to sleep and its disorders has demonstrated significant promise in elucidating the basic mechanisms and functions of sleep and its disorders. As this knowledge base has evolved from multiple trends and disciplines in science and clinical sleep medicine, it is anticipated that new advances in each of these areas will lead to subsequent advances in brain imaging and sleep. It is anticipated that as technology for brain imaging evolves, these methods may eventually be utilized to generate new information regarding treatment mechanisms and will lead to the identification and prediction of treatment response and non-response in clinical sleep medicine. As increasing sample sizes evolve, results from these studies are anticipated to increase our ability to subtype individuals within a disorder based on regional brain function as opposed to an EEG criteria. It is anticipated that future brain imaging studies of sleep will evolve into a more dynamic understanding of brain function across the night. It will be possible not only to describe a person's sleep by means of EEG sleep staging but to categorize an individual's sleep on the basis of the evolution of regional brain function across the night in a type of 3-dimensional moving cerebrohypnogram, a visual movie showing how different regions of the brain are interacting across a night of sleep. Availability of this tool in future research and clinical applications is anticipated to revolutionize our understanding of sleep and its significance in all of human behavior.

Despite advances made to date, significant consideration should also be given to the development of a "Sleep Atlas" imaging resource to facilitate temporal and spatial comparisons of normal waking and sleep, and to assess the effect of factors such as age and cortical thickness across the entire lifespan. The resource would also facilitate functional imaging studies of those with sleep disorders and identifying the most important biological differences. This would be a significant improvement over existing neuroimaging atlases, which consider population variation but not sleep/wake differences in function.

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Chapter 2

Neuroanatomy and physiology of sleep and wakefulness

Pierre-Hervé Luppi and Patrice Fort

Introduction

In most mammals, there are three vigilance states, which are characterized by clear differences in electroencephalogram (EEG), electromyogram (EMG), and electro-oculogram (EOG) recordings. The waking state is characterized by high-frequency, low-amplitude activity on the EEG, sustained EMG activity, and ocular movement; non-rapid eye movement (NREM) or slow-wave (SWS) sleep, is characterized by low-frequency, high-amplitude delta oscillations on the EEG, low muscular activity on the EMG, and no ocular movement; and rapid eye movement (REM), or paradoxical sleep (PS) is characterized by an activated low-amplitude EEG similar to the waking EEG, but with complete disappearance of muscle tone and ocular movements.

Despite a wealth of neuropathological evidence dating back to the nineteenth century indicating that altered states of vigilance can be induced by focal brain lesions and that different neurochemical mechanisms are responsible for the succession of the three vigilance states across 24 h [1], the mechanisms underlying the switch of cortical activity from an activated (desynchronized) state during waking to a synchronized state during deep NREM and then to the activated state of PS have not yet been precisely described.

This chapter examines possible neuronal networks and mechanisms responsible for the switch from waking to NREM and REM sleep.

Mechanisms involved in waking

The activated cortical state during waking is induced by the activity of multiple waking neurochemical systems. Some of these belong to the ascending reticular activating system [2]. These include the serotonergic neurons which are mainly localized in the dorsal raphe nucleus, noradrenergic neurons in the locus coeruleus, and cholinergic neurons in the brainstem, while others are located more rostrally in the forebrain. These correspond to the cholinergic neurons in the basal forebrain, the histaminergic neurons localized in the tuberomammillary nucleus, and the orexin (hypocretin) systems in the tuberal hypothalamus [1].

Altogether, these systems control arousal characterized by high-frequency, low-amplitude cortical activation [3] and widely project to the thalamus and/or the neocortex. When these waking systems are removed, the thalamocortical network oscillates in the delta range (i.e, the slow-wave mode of activity typical of NREM sleep) [1].

During sleep, it is believed that these waking systems are all inhibited by gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. Indeed, it has been shown that the serotonergic neurons of the dorsal raphe nucleus and the noradrenergic neurons of the locus coeruleus are inhibited by GABA during SWS and paradoxical sleep [4, 5]. However, this is yet to be demonstrated for the other waking systems.

Gervasoni and colleagues [5] demonstrated that the unit activity of a single serotonergic neuron shows activity during waking, decreases its activity until it is nearly silent during NREM sleep, and is completely silent during REM sleep. Furthermore, by the localized application of bicuculline, a competitive antagonist of $GABA_A$ receptors, they demonstrated that these neurons ceased or decreased firing during sleep because they are tonically inhibited by GABA. Indeed, application of bicuculline during SWS and PS restored the waking activity of the neurons. Similar results had previously been obtained in noradrenergic neurons in the locus coeruleus [4].

Mechanisms involved in NREM (slow-wave sleep, SWS)

In contrast to the complex and extensive neurochemical network involved in waking, the neurons inducing SWS are localized in the lateral preoptic area and the adjacent basal forebrain. A cluster of these neurons is localized in a small nucleus called the ventrolateral preoptic nucleus (VLPO), which is situated above the optic chiasm. It has been demonstrated in rats that lesions including the VLPO induce insomnia for up to several weeks, with the reduction in the number of sleep-positive cells in the VLPO cluster linearly correlated with the reduction in the quantity of SWS and delta power [6].

GABAergic neurons projecting to the waking systems are localized in the VLPO as well as two brainstem structures, the ventrolateral periaqueductal gray and the dorsal paragigantocellular reticular nucleus [1]. The GABAergic neurons of the VLPO are active specifically during SWS [7, 8]. Sherin and

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colleagues [9] identified a population of neurons in the VLPO that showed expression of the proto-oncogene c-Fos, a marker of neuronal activation [10], in previously sleep-deprived rats following recovery sleep. The greatest density of c-Fos-immunoreactive neurons after SWS increase were localized in the VLPO and the number of c-Fos-immunoreactive cells was directly proportional to the number of minutes of sleep during the hour before the animal was killed. This was confirmed in studies using unit recordings which demonstrated that most of the neurons in this area were specifically activated during sleep compared with the waking state [8]. Neuronal discharge, examined using a chronic microwire technique in rats, demonstrated that VLPO neurons displayed significantly elevated mean discharge rates during NREM sleep compared with waking and that discharge rates progressively increased from light to deep NREM sleep [8].

Switching from waking to NREM sleep

Figure 2.1 compares the neuronal networks responsible for waking, SWS, and paradoxical (REM) sleep. It is thought that the switch from waking to NREM sleep results from the inhibition of the waking systems by the VLPO sleep-active GABAergic neurons. Intracellular recordings in rat brain slices revealed that the VLPO comprises two cell types [11]. Two-thirds of the neurons within the VLPO were homogeneous multipolar triangular-shaped cells that showed a potent low-threshold spike. Moreover, single-cell RT-PCR showed that these cells contain mRNA for glutamic acid decarboxylase (GAD) 65 and 67, the enzymes necessary for the synthesis of GABA, proving that these neurons are of GABAergic type [11].

Based on all data available, a reciprocal interaction of wake-promoting and sleep-promoting neurons across the sleep/waking cycle has been suggested. This theory is supported by in vitro pharmacological studies in rat brain slices which revealed that VLPO neurons are indeed inhibited by most of the waking transmitters [11]. Indeed, extracellular infrared videomicroscopy demonstrated that all of the triangular multipolar neurons of the VLPO are postsynaptically inhibited by norepinephrine and acetylcholine [11]. However, serotonin postsynaptically inhibited only 50% of the neurons previously shown to be inhibited by norepinephrine and acetylcholine and excited the remaining half, suggesting the presence of two distinct subpopulations of cells (types 1 and 2). Histamine and hypocretin had neither inhibitory nor excitatory effects.

Further in vitro pharmacological investigations revealed that VLPO neurons are excited by adenosine A_{2A} agonists [12]. This study examined the hypothesis that adenosine can activate VLPO neurons via adenosine A_{2A} receptors in rat brain slices. Interestingly, the results showed that only the type-2 subpopulation of VLPO neurons that were previously shown to be excited by serotonin were excited by adenosine via postsynaptic activation of the adenosine A_{2A} receptors. Since both adenosine and serotonin progressively accumulate during waking, the authors of the study proposed that the type-2 VLPO neurons, which appear to respond to circadian and homeostatic signals by increasing their firing, may be involved in sleep induction, whilst the type-1 neurons are most likely to play a role in the consolidation of sleep.

To summarize, in the waking rat the hypocretin neurons, for example, may be the first to start firing during waking, exciting all the other waking systems (the basal forebrain cholinergic system; the histaminergic neurons; the monoaminergic, serotonergic, and cholinergic neurons). In turn, these waking systems activate the thalamus and/or the cortex, leading to cortical activation and also, importantly, inhibit the GABAergic sleep-active neurons in the VLPO (Figure 2.1A).

At the onset of sleep, the GABAergic sleep neurons of the VLPO are activated by the circadian clock, localized in the suprachiasmatic nucleus, and the hypnogenic factor adenosine, which progressively accumulates in the brain during waking. It is the effect of this accumulation of adenosine that is the target for one of the most commonly used psychoactive drugs, caffeine [13], which acts via antagonism of the adenosine receptor. In turn these sleep-active neurons begin to inhibit the wake-active neurons in the multiple arousal centers via the neurotransmitter GABA, leading to synchronization of the thalamocortical network (Figure 2.1B). The decreases in sensory inputs is also necessary to let sleep occur since waking systems are excited by them.

Mechanisms involved in paradoxical (REM) sleep

It was first shown that PS persists following decortication, cerebellar ablation, or brainstem transections rostral to the pons. In contrast, transection at the posterior limit of the pons suppressed PS [14]. It was then demonstrated that a state resembling PS is still visible in the "pontine cat," a preparation in which all the structures rostral to the pons have been removed [14]. These results indicated that brainstem structures are necessary and sufficient to trigger and maintain the state of PS, a concept still valid today. By using electrolytic and chemical lesions, it was then evidenced that the dorsal part of the pontis oralis (PnO) and caudalis (PnC) nuclei contains the neurons responsible for PS onset [14]. Furthermore, bilateral injections of a cholinergic agonist, carbachol, into the dorsal area of the PnO and PnC, also named peri-locus coeruleus α (peri-LCα), the pontine inhibitory area (PIA), and the subcoeruleus nucleus (SubC) in cats, and more recently the sublaterodorsal tegmental nucleus (SLD) in rats, dramatically increases PS quantities [15, 16]. It was then shown by unit recordings in freely moving cats that many SLD neurons show a tonic firing selective to PS (called "PS-on" neurons) [17, 18]. It was thought that SLD PS-on neurons are cholinergic until we recently showed that they are glutamatergic.

First, in contrast to cats, carbachol iontophoresis into the rat SLD, the equivalent of the cat peri-LCα, induces waking (W) with increased muscle activity [19]. Further, only occasional cholinergic neurons were stained for c-Fos in the laterodorsal tegmental nucleus (LDT), pedunculopontine tegmental nucleus (PPT) and SLD after PS hypersomnia [20]. Finally, in rats,

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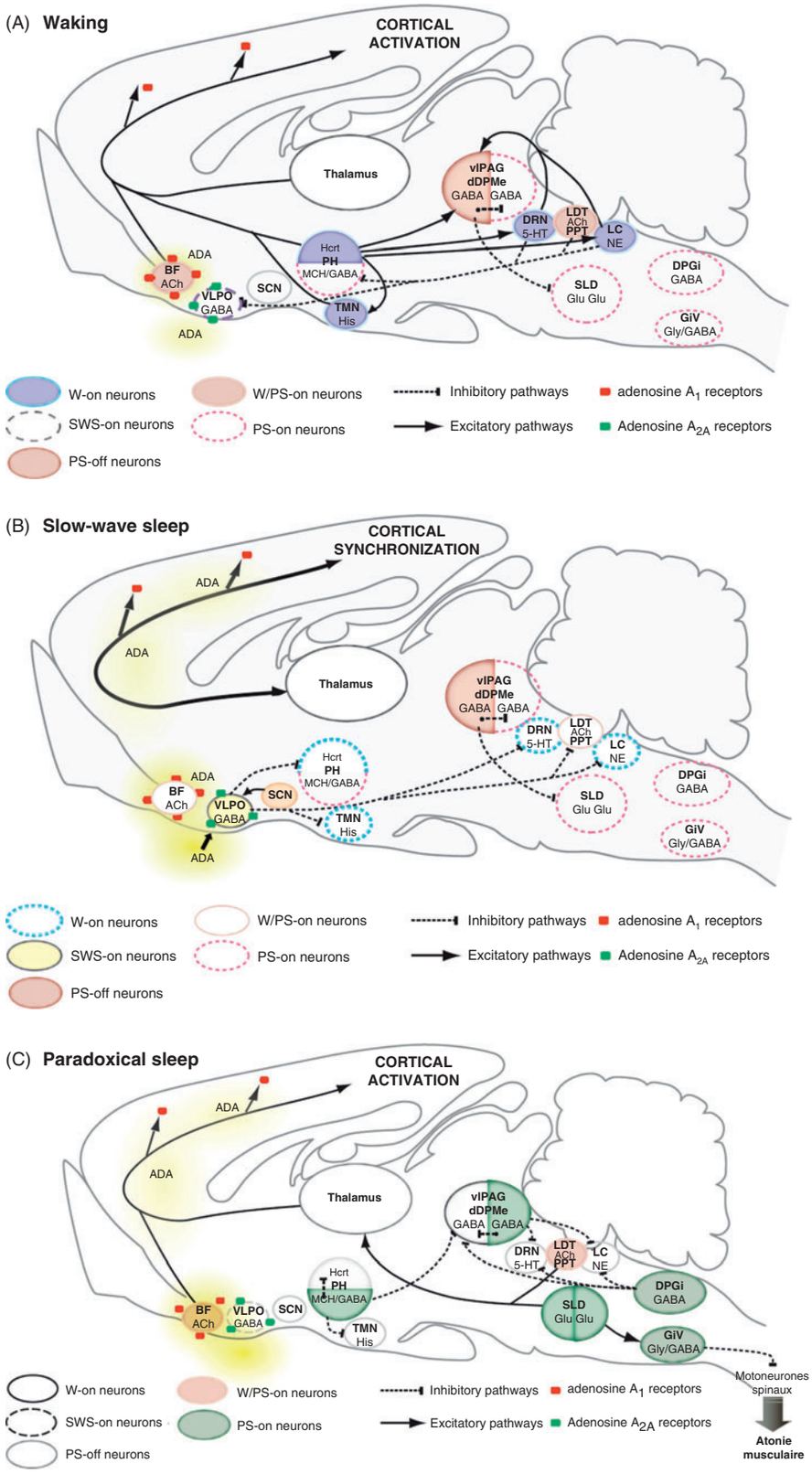

Figure 2.1 Neuronal networks responsible for waking, slow-wave (non-rapid eye movement [NREM]) sleep and paradoxical (REM) sleep (adapted from Fort *et al.* [1]). Abbreviations: 5-HT = 5-hydroxytryptamine (serotonin), ACh = acetylcholine; ADA = adenosine; BF = basal forebrain; DPGi = dorsal paragigantocellular reticular nucleus; dDPMe = deep mesencephalic reticular nucleus; DRN = dorsal raphe nucleus; GABA = gamma-aminobutyric acid; GiV = ventral gigantocellular reticular nucleus; Glu = glutamate Gly = glycine; Hcrt = hypocretin (orexin)-containing neurons; His = histamine; LC = locus coeruleus; LDT = laterodorsal tegmental nucleus; MCH = melanin concentrating hormone-containing neurons; NE = norepinephrine; PH = posterior hypothalamus; PPT pedunculopontine tegmental nucleus; PS = paradoxical sleep; SCN = suprachiasmatic nucleus; SLD = sublaterodorsal nucleus; SWS = slow-wave sleep; TMN = tuberomamillary nucleus; vlPAG = ventrolateral periaqueductal gray; VLPO = ventrolateral preoptic nucleus; W = waking.

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