134

SLEEP DISTURBANCES ASSOCIATED WITH NEUROPSYCHIATRIC DISEASE

ERIC A. NOFZINGER MATCHERI KESHAVAN

Several observations suggest important links between sleep and mental disorders. From a psychological perspective, it has long been thought that trouble sleeping is related to a troubled mind, an intrusion of mental activity into the quiescence of sleep. Historically, this vein has fueled much of the interest in the relationship between sleep and mental disorders until the discovery of electrophysiologically defined sleep stages, particularly rapid eye movement (REM) sleep in the 1950s. Even after that time and into the 1960s and 1970s, this basic psychological tenet guided interest in uncovering relationships between REM sleep and mental disorders. Over time, interest shifted to defining the neurobiology of mental disorders. In this service, EEG sleep staging became a tool to be used in either diagnosis or validation of the biological nature of mental disorders. A second, nonpsychiatric, line of investigation during this time concerned itself with the physiology of normal sleep. This led to a significant expansion in our understanding of the brain mechanisms that govern basic sleep/wake, or behavioral state, regulation. Few attempts, however, have been made to bridge these diverging lines of investigation despite the complimentary information derived from each area. In part, this may be related to the vastly divergent levels of observation of the brain capable in preclinical and human studies. With the advent of advances in preclinical work defining the brain mechanisms underlying electrophysiologic oscillations measured at the brain surface and in human brain imaging work defining correlates of underlying functional neuroanatomy, these divergent fields are beginning to communicate in meaningful ways to enrich the discoveries made in each domain. Evidence of this evolution comes in the form of chapters in this volume devoted to neuropsychopharmacology by neuroscientists such as Allan Hobson and Emmanuel Minot and the inclusion in this clinical chapter of preclinical data that may guide interpretations of human electrophysiology and functional neuroanatomy.

As a guide, this chapter attempts to first distill aspects of preclinical work that may inform our understanding of findings in electrophysiology and functional neuroanatomy in clinical populations. We then review the subjective, EEG, and brain imaging work in the major mental disorders that help to define pathophysiology through a sleep window into brain function. Disorders that are highlighted are the major mood disorders, schizophrenia, and degenerative disorders of aging given the extensive sleep research conducted in each of these areas.

NEUROBIOLOGY OF HEALTHY SLEEP

Overview of the Sleep/Wake Cycle

Sleep can be conceptualized as a motivated behavior, something the organism "needs" to do in order to survive and for which there is a pressure to perform. Sleep propensity is lowest shortly after awakening, increases in mid-afternoon, plateaus across the evening, is greatest during the night and declines across sleep. Sleep has been subclassified polysomnographically into NREM and REM sleep states based on three measures: (1) electroencephalography (EEG), (2) electromyography (EMG), and (3) electrooculography (EOG). With sleep onset, the EEG frequency slows, the amplitude increases and the EMG decreases. This sleep is classified as NREM stages 1, 2, 3, or 4, which are distinguished by increasing amounts of low-frequency, high-amplitude EEG activity, also known as "delta" activity. Delta sleep decreases across the night. REM sleep follows the first NREM period and is characterized by low-amplitude, mixed high-frequency EEG, the occurrence of intermittent REMs, skeletal muscle atonia, and irregular cardiac and respiratory events. Across the night, brain function oscillates between the globally distinct states of NREM and REM sleep about three or four times, approximately every 90 minutes. Across successive sleep cycles within a night, stages 3 and 4 sleep de-

Eric A. Nofzinger and Matcheri Keshavan: Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

crease and then disappear, whereas REM sleep and lighter NREM sleep stages increase.

Historical Development of Sleep Neurobiology

The current understanding that sleep and wakefulness are both active brain states that are generated and maintained from within the brain has its origins in the pioneering work of Berger (1930), Economo (1929), Bremer (1935), Moruzzi and Magoun (1949), and Jouvet (1962). Prior to the work of these investigators, the state of sleep was thought to represent an inactive period for the brain. Berger first described electrophysiologic patterns of brain electrical activity that correlated with changes in behavioral state. Other investigators discovered that the brain itself was responsible for generating its own intrinsic electrical activity and for switching between behavioral states. Clinicoanatomic clues came in the discovery by Economo (1929) that lesions to the posterior hypothalamus in encephalitis lethargica produced somnolence or coma, suggesting a role for the posterior hypothalamus in maintaining wakefulness. Moruzzi and Magoun defined the concept of a nonspecific ascending reticular activating system (ARAS) responsible for cortical activation following their discovery that electrical stimulation of the brainstem reticular formation suppressed highamplitude EEG waves in the cortex. Finally, following the discovery of the behavioral state of REM sleep by Aserinsky and Kleitman (1), the French neurophysiologist Michel Jouvet (2) localized the generation of this sleep state to structures in the pontobulbar brainstem using rostropontine transections in cats. From these studies it is now recognized that behavioral state is intrinsically regulated and generated by the brain itself and manifested by electrical activity in the brain that can be recorded by EEG at the scalp.

An extensive preclinical literature has developed that describes the brain mechanisms of the distinct electrophysiologic oscillations that characterize the various behavioral states of waking, NREM, and REM sleep. Several features are important with respect to localizing the brain structures underlying slow wave sleep. First, the electrical oscillations observed at the macroscopic level are the end result of electrical oscillations involving widespread thalamocortical neurons that are synchronized in a global fashion. Second, widespread changes in these oscillations can result from state-dependent changes in modulatory systems such as the brainstem, hypothalamus, and basal forebrain. Third, slow oscillations in the 1 to 4 Hz delta range have both cortical and thalamic components. This line of research emphasizes that rhythmic oscillations are the end result, therefore, of integrated corticothalamic circuits and modulatory structures. Changes in delta sleep found in diverse neuropsychiatric disorders, therefore, may result from functional changes at one or more levels including the cortex, thalamus, and modulatory structures.

At the other end of the oscillatory spectrum are the fast oscillations in the beta and gamma frequencies (roughly > 20 Hz) that have been associated with increased vigilance and are most prevalent during waking and REM sleep (3, 4). These fast rhythms are present in cortical and thalamic neurons and depend on neuronal depolarization characteristic of brain activation, a state in which neurons are maximally ready to respond to either external (in waking) or internal (in REM sleep) stimuli. These fast synchronous rhythms may serve a purpose of binding aspects of a stimulus into a global representation. Importantly, these fast rhythms as well as the slow rhythms are dependent on the level of excitability in local intracortical circuits as may be modulated by ascending activating modulatory systems such as the brainstem monoaminergic and cholinergic nuclei (5). Disturbances in these fast frequency oscillations in neuropsychiatric disorders may reflect pathology at one or more of these levels modulating these electrophysiologic rhythms.

Mechanisms Underlying Behavioral State Changes: Core Structures Related to Arousal

From the electrophysiologic preclinical literature, it has become apparent that the set point for electrical oscillations in widespread thalamocortical circuits can be modulated by global ascending activating influences. Identification of the structures that are important in providing this input, therefore, may provide clues as to the brain mechanisms leading to altered electrophysiologic activity in diverse neuropsychiatric disorders. Arousal and the maintenance of an aroused state is an active process requiring the integrated activity of a series of arousal systems shown diagrammatically in Fig. 134.1. (See Robbins and Everitt, 1996, for review and Moore and colleagues, 2001, for a discussion of the relationship between the Orexin neurons and these arousal systems) (6,7).

The central brainstem arousal system is the ascending reticular activating system (ARAS) (8,9). The ARAS projects into a series of specific brainstem systems including the pontine cholinergic nuclei, midbrain raphe nuclei, and the locus ceruleus, and into a series of forebrain structures involved in arousal. These include the midline and medial thalamus with widespread cortical projections and the amygdala, which has interconnections with isocortex and other areas involved in arousal, particularly hypothalamus and ventral striatum. The amygdala is particularly involved with autonomic regulation and the emotional component of arousal. There are two important components of the basal forebrain-ventral striatum system (10). One is the cholinergic neurons of the medial septum-nucleus of the diagonal band-nucleus basalis complex that innervates the entire forebrain. The second is the nucleus accumbens-ventral striatum complex that is involved in transmitting the arousing aspects of reinforcing stimuli. Until recently, the impor-



FIGURE 134.1. Arousal systems in the human brain (see text for description). The transmitters associated with each system are abbreviated. ACH, acetylcholine; DA, dopamine; GABA, γ aminobutyric acid; GLU, glutamate; HIST, histamine; HYP, hypocretin; NA, noradrenaline; 5HT, serotonin.

tance of the hypothalamus was not fully recognized, but this is rapidly changing (10,11). First, we now appreciate that an important component of the circadian control of behavioral state is the maintenance of arousal by the circadian pacemaker, the suprachiasmatic nucleus (12). Second, there are extensive hypothalamic projections to isocortex, predominantly from posterior hypothalamus. These include a newly discovered projection from a group of neurons that produce a novel peptide hypocretin. This projection is of particular interest because the hypocretin neurons project not only over the entire isocortex but also to all of the arousal systems noted in Fig. 134.1, including extraordinarily dense projections to locus ceruleus, raphe nuclei, pontine cholinergics, midline thalamus, nucleus basalis, and amygdala. (See ref. 7 for review.) The hypocretin projection has become of particular interest because a hypocretin gene knockout produces a narcolepsy-like syndrome in mice (13) and hypocretin is below detectable levels in CSF from narcoleptics in comparison to controls (14).

Mechanisms Underlying Behavioral State Changes: Core Structures Involved in REM Sleep

The nature of dreaming has led to extensive discussions about the relationships between REM sleep and mental disorders (9). The finding of EEG sleep staging abnormalities in REM sleep in certain mental disorders has also fueled discussions about the relationships between the biology of REM sleep and the pathophysiology of mental disorders; therefore, a brief review of brain structures that may have overlapping roles in REM sleep regulation and the pathophysiology of mental disorders may guide theoretical models of behavioral state regulation in diverse mental disorders (see Chapters 128 to 133). Evidence from a variety of approaches suggests that the laterodorsal and pedunculopontine tegmental cholinergic nuclei (LDT and PPT) in the

pontine reticular formation underlie the phasic and tonic components of REM sleep (9). A reciprocal interaction hypothesis (9) claims that these cholinergic nuclei become disinhibited during the entry into REM sleep by the removal of tonic inhibition from noradrenergic and serotonergic nuclei as these monoaminergic nuclei slow or become silent in the transition from NREM to REM sleep (15). Modifications of this model now account for the influence of additional brainstem neurotransmitter systems such as GABAergic, nitroxergic, glutamatergic, glycinergic, histaminergic, adenosinergic, and dopaminergic; various peptide systems such as galanin, Orexin, vasoactive intestinal polypeptide, and nerve growth factor; and hormonal influences such as growth hormone-releasing hormone, prolactin, and corticotropin-releasing factor (9,11,16-18). Brainstem reticular nuclei include a dorsal pathway innervating the thalamus and a ventral pathway innervating the basal forebrain that thereby mediates widespread cortical arousal indicative of the REM sleep state. Human brain imaging studies of REM sleep show that the ventral pathway predominates during human REM sleep in activating anterior paralimbic structures (19,20).

Mechanisms Underlying Behavioral State Changes: Modulatory Structures

In large part, these preclinical studies have focused on the primary nuclei that may be generative centers for one behavioral state or another. Less information is available regarding structures that modulate activity in these centers and that may play a role in the abnormal modulation of behavioral states in various mental disorders (8,9). Recent work, for example, suggests that the amygdala has significant anatomic connections and recently established modulatory effects on the brainstem centers involved in REM sleep production (21,22). Similarly, other forebrain structures such as the hypothalamus (13) and basal forebrain (10,17) are

known to have both anatomic and functional relationships with brainstem centers thought to play a role in behavioral state regulation in addition to the primary roles they each play in cortical arousal. Although it is possible that certain disease states are associated with pathologic changes in discrete brain structures that generate discrete behavioral states, it is more likely (e.g., in the case of depression) that there are pathologic functions in brain structures that have modulating effects on these core brain structures in producing the behavioral state changes.

Mechanisms Underlying Behavioral State Changes: Evidence from Human Sleep Imaging Studies

The advent of brain imaging methods that can be used to study the functional neuroanatomy of human sleep has recently created a venue for linking preclinical work with human sleep electrophysiology. Findings from these new studies have enriched our understanding of the brain structures that are preferentially active across behavioral states and that may play a role in behavioral state regulation as well as functional roles for discrete behavioral states.

Global Changes in Brain Function across Behavioral States

In terms of global, or whole brain changes, from waking to NREM sleep, there are reductions in measures of cortical blood flow or metabolism (19). During REM sleep, global blood flow or metabolism ranges from 10% below to 41% above levels obtained during wakefulness (23,24). A recent report cited a positive correlation between waking global and regional cerebral blood flow and slow wave sleep measures from the subsequent night of sleep (25). The authors interpreted these findings as reflecting an energy conservation or restorative role for slow wave sleep.

Relative Regional Changes during NREM Sleep

In terms of regional relative changes during NREM sleep, blood flow has been shown to negatively correlate with the presence of NREM sleep in the anterior cingulate (19,26, 27), pontine reticular formation (19,26,27), thalamus (19, 26–28), basal forebrain/hypothalamus (19,26), amygdala (26), and orbitofrontal cortex (19,26,27). These changes are consistent with preclinical studies showing reductions in brainstem, basal forebrain, and hypothalamus sources of ascending activation. Declining function in the amygdala suggests the possibility that this structure modulates activity in ascending activating structures.

Relative Regional Changes during REM Sleep

In terms of regional relative changes during REM sleep, this state has been reliably associated with the selective activation

of limbic and paralimbic structures including the amygdala, ventral striatum, anterior cingulate, and medial prefrontal cortex (19,20,23,29,30). This pattern of activation is superimposed on brainstem activation known to play a role in REM sleep generation on the basis of preclinical work.

Functional Brain Changes Associated with Sleep Deprivation

Several studies have discovered that sleep deprivation is associated with a global reduction in metabolism with some preference for the prefrontal cortex. This reduction is magnified with successive nights of sleep deprivation. These changes have recently been shown to play a role in the cognitive alterations associated with sleep deprivation (31).

THEORETICAL MODELS OF THE FUNCTION OF SLEEP

Homeostatic Function

Several models of sleep/wake regulation attempt to define parameters that may influence the probability at any point in the day that sleep may occur. One such model is the two-process model described by Borbely (32). One process, called process S, describes a homeostatic sleep process. Process S is thought to be dependent on the amount of prior wakefulness and is reflected by the amount of EEG slow wave (.5 to 4.5 Hz EEG) activity. As sleep deprivation increases, for example, process S increases and amplifies sleep propensity. The second process, process C, varies throughout the day in relation to a sinusoidal circadian phase across a 24-hour day. The intensity of this sleep propensity is unrelated to the amount of prior wakefulness. The sleep parameter most affected by this process is process C; nonsleep correlates of this process include core body temperature, plasma melatonin, and plasma cortisol levels. The regulatory structure for this process is the suprachiasmatic nucleus.

Sleep and Neuronal Plasticity

Several theorists have conceptualized distinct roles for the diverse sleep/wake states based on emerging knowledge regarding forebrain function in information processing. Buzsaki (33) emphasized a two-stage model of waking hippocampal memory trace formation and suggested parallels for two stages of memory processing during NREM and REM sleep. Karni and associates and Wilson and McNaughton have demonstrated direct evidence in support of memory processing during sleep for REM and NREM sleep, respectively.

Although the general states of neuronal activation have been described for NREM and REM sleep, little is known within these states about the relevance of this neuronal activation. Llinas and Pare (34) suggest that wakefulness and REM sleep are fundamentally equivalent states of activation characterized by intrinsic oscillatory thalamo-cortical loops differing only in the degree to which external stimuli are capable of modulating the global brain state. They suggest that these oscillations serve the purpose of generating an internal representation of the world guided by innate predispositions of the brain to categorize and integrate the sensory world in certain ways. During REM sleep, these innate templates, which have been molded by experience, may be used to recreate world-analogues. During wakefulness, these templates are modulated by sensory events. Winson (35) suggested that, in humans, psychological experience essential to survival is integrated and further consolidated during REM sleep. He based this hypothesis on: (a) the presence of hippocampal theta during REM sleep; (b) the sole occurrence of hippocampal theta during species-specific survivaldependent behavior in nonprimates; and (c) the role of hippocampal theta in the induction of long-term potentiation (LTP), a model for the synaptic modulation underlying certain types of memory. Kavanau (36), reviewing data on synaptic events related to the formation of enhanced synaptic efficacy in the context of evolutionary biology, suggests that REM sleep may perform the service of repetitive activations of synapses in neural circuits that underlie essential adaptive behaviors. This "dynamic stabilization" is thought to ensure the efficacy of circuits that otherwise may suffer from a disuse atrophy. Although clearly these hypotheses require validation, the underlying premises are consistent with psychological theories that REM sleep and dreaming may play a role in affective adaptation; in the integration of recent, remote, and perhaps phyletic memory; maintaining or facilitating behavioral repertoires underlying crucial behavior; and the genetic programming of inherited behavior.

SLEEP IN MAJOR NEUROPSYCHIATRIC DISEASES

We turn now to characterizing the sleep disturbances in the major mental disorders. The vast majority of relevant data come from clinical and EEG sleep reports. Early findings from functional brain imaging studies are also reviewed.

DEPRESSION

Subjective Findings

The majority of patients with mood disorders describe difficulty falling asleep, staying asleep, and returning to sleep after early morning awakenings. Clinically, they report a paradoxic state of physical daytime fatigue, yet with persistent mental activity that makes it difficult for them to fall asleep at night. Subjective sleep quality has been measured with a validated instrument called the Pittsburgh Sleep Quality Index (PSQI) (37). In one study, subjective sleep quality was rated worse by patients with major depression than by patients presenting with a chief complaint of insomnia or other sleep disorder patients. Whereas insomnia characterizes the melancholia of middle age and elderly unipolar depression, younger patients and bipolar depressed patients often describe, atypically, difficulty getting up in the morning and hypersomnia during the daytime. This subjective hypersomnia, however, does not translate into an increased physiologic tendency to fall asleep when measured objectively by the Multiple Sleep Latency Test (MSLT).

EEG Findings

An extensive literature describes the changes in EEG sleep in patients with depression (38,39). Measures derived from the EEG sleep recordings that have been found to differ between healthy and depressed subjects include measures of sleep continuity, measures of visually scored EEG sleep stages, and automated measures of characteristics of the EEG waveform across the sleep period such as period amplitude or EEG spectral power measures.

The changes in subjective sleep complaints are paralleled by EEG measures of sleep. These include increases in sleep latency and decreases in sleep continuity. In terms of EEG sleep stages or "sleep architecture," depressed patients often show reduced stage 3 and 4 NREM sleep (also known as "slow wave sleep" because of the presence of slow EEG delta activity during these stages). Several changes in REM sleep also have been noted. These include an increase in the amount of REM sleep, shortening of the time to onset of the first REM period of the night, shortened REM latency, and increase in the frequency of eye movements within a REM period.

In terms of quantitative EEG changes in sleep, many (40,41) but not all studies have reported reductions in the amplitude or a reduction in the number of low frequency (0 to 4 Hz) delta waves during sleep in depressed patients. Increased high frequency EEG activity has also been reported in depressed patients, including alpha (40) and beta. Importantly, sex differences have been found in these abnormalities. Depressed women appear to have relative preservation of delta sleep in relation to depressed men, despite elevations in higher frequency EEG activity in both groups (42).

Several observations regarding sleep disruption in depressed patients suggest that there may be a timing abnormality in the evolution of sleep across the night in depressed patients (38,41). A number of factors can influence the sleep EEG findings characteristic of depression. For instance, sleep continuity deteriorates, slow wave sleep decreases, and REM latency shortens with age, even in healthy subjects; however, age-related changes are more pronounced in patients with depression (43). By contrast, sleep EEG measures are generally less abnormal in adolescents and prepubertal children with depression, and only appear consistently in those adolescents who are hospitalized and/ or suicidal (44).

Other studies have shown that patients with psychotic depression have particularly severe EEG sleep disturbances and very short REM sleep latencies; patients with recurrent depression have more severe REM sleep disturbances than patients in their first episode; and sleep continuity and REM sleep disturbances are more prominent early in the depressive episode than later (45). Some studies suggest that patients with dysthymia and mania (surprisingly) have EEG sleep disturbances very similar to those observed in major depression.

Stressful life events also interact with EEG sleep. For instance, individuals who have severe stressful events preceding the onset of depression are less likely to have reduced REM latency than patients without such a stressor. Among older depressed patients, poor sleep is associated with shorter episode duration, older age, greater medical burden, the presence of life stressors, and a lower level of perceived social support (45).

EEG sleep findings help to inform our understanding of the neurobiology of longitudinal course and treatment outcome in depression. Although severely reduced REM latencies, phasic REM measures, and sleep continuity disturbances generally move toward control values after remission of depression, most sleep measures show high correlations across the course of an episode. Reduced REM latency is associated with increased response rates to pharmacotherapy (46) but not psychotherapy. Depressed patients with abnormal sleep profiles (reduced REM latency, increased REM density, and poor sleep continuity) are significantly less likely to respond to cognitive behavior therapy and interpersonal therapy than patients with a "normal" profile. Other studies have indicated that reduced REM latency and decreased delta EEG activity are associated with increased likelihood or decreased time until recurrence of depression in patients treated with medications or psychotherapy (47).

Sleep Neuroendocrine Findings

Cortisol secretion has been linked with the circadian cycle and growth hormone with slow wave sleep processes. In depressed subjects, studies have shown increases in cortisol secretion rates, a flattening of the circadian rhythms in cortisol, and elevated cortisol nadir. Secretion of growth hormone on the other hand, is reduced in the first half of the night in depressed subjects both in the acute phase and following remission from depression. Evidence such as this has been used to support hypotheses that a balance between the oppositional actions of CRF and GHRH may be shifted toward CRF in major depression. Given the activating qualities of CRF and its direct or indirect inhibition of GHRH, sleep would be shifted toward states of cortical activation, that is, either waking or REM sleep, and away from NREM sleep, which has been associated with the homeostatic function of sleep.

Sleep Neuropharmacologic Findings

Each of the major neurotransmitter systems shown to modulate the ascending activation of the cortex, that is, the cholinergic, noradrenergic, and serotonergic systems, have been implicated in the pathophysiology of mood disorders. The role of additional brainstem neurotransmitter systems such as GABAergic, nitroxergic, glutamatergic, glycinergic, histaminergic, adenosinergic, dopaminergic, and various peptide systems such as galanin, Orexin, vasoactive intestinal polypeptide, and nerve growth factor in the sleep disturbances in depression remain to be defined. Nearly all effective antidepressant medications show a pronounced inhibition of REM sleep including a prolongation of the first REM cycle and a reduction in the overall percent of REM sleep. (Exceptions include nefazodone [48] and bupropion, which do not suppress REM sleep [49].) Enhanced cholinergic function concurrent with reduced monoaminergic tone in the central nervous system has been proposed as a pharmacologic model for depression. In an exaggerated sense, the state of REM sleep mimics this formulation, that is, a cholinergically driven state with reduced firing of noradrenergic and serotonergic neurons. Cholinergic agents such as the muscarinic agonist RS 86, arecoline, physostigmine, and scopolamine produce exaggerated REM sleep effects in depressed patients in comparison with patients with eating disorders, personality disorders, anxiety disorders, and healthy controls (50). These studies suggest that there may be a supersensitivity of the cholinergic system driving REM sleep in mood disorders patients, although an alternative plausible hypothesis is that there may be reduced monoaminergic (5-HT and/or NE) inhibition of the brainstem cholinergic nuclei in mood disorders patients. Cholinergic activation may also play a role in the hyperactivity in the HPA axis and in the blunting of growth hormone secretion noted in depressed patients across the night, given the influence of cholinergic drugs on HPA activity and GH release.

Selective serotonin reuptake inhibitors are known to have prominent REM suppressing activity, most notably early in the night when enhances in REM sleep are most often seen in mood disorders patients (39). A tryptophan-free diet, which depletes central serotonin activity, is noted to decrease REM latency in healthy controls and in depressed patients (51) and ipsapirone, a 5-HT1a agonist, is noted to prolong REM latency in both normal controls and in depressed patients (52). Anatomically, 5-HT1a receptors have been conceptualized as the limbic receptors given their high densities in the hippocampus, septum, amygdala, and cortical paralimbic structures. The action in these structures has been shown to be largely inhibitory (hyperpolarizing). Given the importance of limbic and paralimbic structures in REM sleep modulation, the influence of SSRI medications may be mediated by these limbic receptors. Importantly, in the brainstem LDT, a locus of cholinergic cells identified in the generation of REM sleep, bursting cholinergic neurons are inhibited by the action of 5-HT on 5-HT1a receptors. Finally, the effects of the 5-HT1a-antagonist pindolol on EEG sleep in healthy subjects was studied and noted to reduce REM sleep. This was interpreted as supportive of a reduction in raphe serotonergic autoregulation, resulting in increased serotonergic input to pontine cholinergic centers and inhibiting REM sleep.

Functional Neuroimaging Findings

Given the selective activation of limbic and paralimbic structures during REM sleep in healthy subjects, the study of the functional neuroanatomy during REM sleep in depressed patients may provide clues as to alterations in limbic and paralimbic function related to the pathophysiology of depression. In contrast to healthy controls (4), depressed patients fail to activate anterior paralimbic structures (subgenual and pregenual anterior cingulate and medial prefrontal cortices) from waking to REM sleep. In contrast to healthy controls, depressed subjects show large activations in the dorsal tectum (superior colliculus and periaqueductal gray) during REM sleep. Finally, in contrast to controls, depressed subjects activate left sensorimotor cortex, left inferior temporal cortex, left uncal gyrus and amygdala, and left subicular complex during REM sleep. These findings suggest that depressed patients demonstrate uniquely different patterns of activation from waking to REM sleep than do healthy controls. In the context of neuroscience models relating forebrain function during REM sleep to attention, motivation, emotion, and memory, these results suggest that prior REM sleep abnormalities in mood disorders patients, therefore, likely reflect alterations in limbic and paralimbic forebrain function related to depression (Fig. 134.2).

Functional neuroimaging of NREM sleep in depressed subjects would be expected to provide evidence regarding the functioning of homeostatic mechanisms in mood disorders patients since this is a time of nonselective nonactivation of the cortex in which the buildup of a sleep dependent process, process S, is discharged and during which growth hormone secretion occurs. Ho and Gillin and colleagues (53) demonstrated that whole brain and regional cerebral glucose metabolism was elevated during the first NREM period of the night for depressed men in relation to healthy men. These findings are supportive of a deficiency of homeostatic mechanisms in mood disorders patients, perhaps secondary to cortical hyperarousal. Clark and associates (25) reported that reductions in delta sleep in depressed patients



FIGURE 134.2. Healthy and depressed subjects' changes in relative glucose metabolism from waking to rapid eye movement (REM) sleep. The top two images are midsagittal sections showing areas of the brain that have greater relative glucose metabolism during REM sleep than during waking. These areas include anteriorly located paralimbic structures such as the ventral striatum, anterior cingulate cortex, and medial prefrontal cortex. The lower two images show the same comparisons, but in depressed patients. Of note is the absence of an increase in relative metabolism in any of these anteriorly located paralimbic structures in depressed patients from waking to REM sleep. See color version of figure.

were associated with reductions in afternoon waking relative and global blood flow. This suggests that the elevations in glucose metabolism during NREM sleep in depressed patients are not related to a waking hypermetabolic state. Studies across waking and NREM sleep are needed in order to clarify this notion.

Nofzinger and associates (54) sought to clarify the neurobiological basis of variations in one aspect of central nervous system "arousal" in depression by characterizing the functional neuroanatomic correlates of beta EEG power density during NREM sleep. First, nine healthy (N = 9) subjects underwent concurrent EEG sleep studies and [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) positron emission tomography (PET) scans during their first NREM period of sleep in order to generate hypotheses about specific brain structures that show a relationship between increased beta power and increased relative glucose metabolism. Second, brain structures identified in the healthy subjects were then used as a priori regions of interest in similar analyses from identical studies in 12 depressed subjects. Statistical parametric mapping was used to identify the relationship between beta power and relative regional cerebral glucose metabolism (rCMRglu) during NREM sleep. Regions that demonstrated significant correlations between beta power and relative cerebral glucose metabolism in both the healthy and depressed subjects included the ventromedial prefrontal cortex and the right lateral inferior occipital cortex. During a baseline night of sleep, depressed patients demonstrated a trend toward greater beta power in relation to a separate age- and gender-matched healthy control group. In both healthy and depressed subjects, beta power negatively correlated with subjective sleep quality. Finally, in the depressed group, there was a trend for beta power to correlate with an indirect measure of absolute whole brain metabolism during NREM sleep. This study demonstrated a similar relationship between electrophysiologic arousal and glucose metabolism in the ventromedial prefrontal cortex in depressed and healthy subjects. Given the increased electrophysiologic arousal in some depressed patients and the known anatomic relations between the ventromedial prefrontal cortex and brain activating structures, this study raises the possibility that the ventromedial prefrontal cortex plays a significant role in mediating one aspect of dysfunctional arousal found in more severely aroused depressed patients.

Wu and associates (55) characterized the functional neuroanatomic changes following sleep deprivation therapy in depressed patients. They found that depressed patients who demonstrated high pretreatment relative glucose metabolic rates in the medial prefrontal cortex were more likely to respond to sleep deprivation. Further, a reduction in relative metabolism in this region was found following sleep deprivation.

Depression and Alcoholism

Significant comorbidity exists between depression and alcoholism. EEG sleep studies have been used as a tool to explore the relationships between the neurobiology of the two disorders. Clark and colleagues (56) found that alcoholism played a more significant role in sleep disruption than depression. Increased REM density in primary alcoholics with and without a lifetime diagnosis of secondary depression predicted 3-month alcohol-related relapse rates. Drummond and coworkers (57) examined the relationships among sleep, natural course, and relapse in abstinent pure primary alcoholic patients. They found that the sleep was short, fragmented, and shallow early in abstinence with some incomplete improvements over the first year of abstinence. Further, the presence of sleep disruption at 5 months was shown to predict relapse by 14 months.

SCHIZOPHRENIA

REM Sleep

Early sleep EEG studies sought to test the intriguing hypothesis that schizophrenia is a spillover of the dream state into wakefulness. No evidence has accrued to support this prediction; however, subtle alterations in architecture of REM sleep may occur. REM latency was found decreased in seven of the 10 studies (58). It has been proposed that this may result from a deficit in SWS in the first NREM period leading to a passive advance, or early onset of the first REM period. An alternative explanation is "REM pressure." However, studies of the amounts of REM sleep have been conflicting with increases, decreases, as well as no change being found (58,59). Studies examining treatment naive schizophrenia patients show no increases in REM sleep (60, 61); the increases in REM sleep observed in previously treated subjects may reflect effects of medication withdrawal and/or changes related to the acute psychotic state (61). It is unlikely that the observed decreases in REM latency in some schizophrenia patients result from primary abnormalities in REM sleep.

Slow Wave Sleep

Slow wave sleep is of particular interest to schizophrenia because of the implication of the prefrontal cortex in this disorder (62) and in generation of SWS (63). Several studies have shown a reduction of SWS in schizophrenic patients; SWS deficits have been seen in acute, chronic, as well as remitted states; and in never-medicated, neuroleptictreated, as well as unmedicated patients (58); however, not all studies show these deficits. Studies that fail to find differences in SWS have generally used conventional visual scoring. Three studies that have quantified sleep EEG parameters have consistently shown reductions in SWS. Ganguli and associates (60) observed no change in visually scored SWS, but instead, a significant reduction in delta wave counts in drug-naive schizophrenic patients, suggesting that visually scored SWS may not be sensitive enough, and automated counts may be a better marker of SWS deficiency in schizophrenia. Other groups have described similar reductions in delta counts. SWS deficits have been recently demonstrated in early course schizophrenia using sensitive approaches such as spectral analysis (64).

Sleep Deprivation Studies

Sleep deprivation provides a naturalistic, physiologic challenge for dynamic manipulation of sleep processes, and can help clarify the primary nature of sleep abnormalities. An intriguing reduction in REM rebound following REM sleep deprivation has been described in several studies in acute schizophrenia, but a normal or exaggerated REM rebound in remitted schizophrenic patients (58). This rebound failure in acute schizophrenia has been attributed to a possible "leakage" of phasic REM events from REM sleep into NREM sleep, although no systematic investigation has supported this hypothesis.

Sleep deprivation studies can also help clarify whether SWS abnormalities in schizophrenia are secondary to pathology in neuronal circuits in this disorder, or whether they reflect primary homeostatic disruption in sleep processes. There is evidence (65) that following total sleep deprivation, recovery of Stage 4 sleep is diminished in schizophrenia. SWS deprivation is known to consistently cause impaired attention, prolonged reaction time, verbal learning, and vigilance similar to what is seen in frontal lobe dysfunction and schizophrenia (66). A defect in SWS recovery might be consistent with impairments in critical cognitive processes such as psychomotor vigilance observed in schizophrenia. Such a defect might also suggest impairment in trophotropic or restorative processes in schizophrenia.

Relation between Sleep Abnormalities and Clinical Measures in Schizophrenia

The neurobiological correlates of the psychopathological dimensions are critical for our understanding of the pathophysiology of psychiatric disorders. Research during the past decade has focused increasingly on the positive and negative syndromes, a conceptual distinction of particular importance to pathophysiology of schizophrenia. A number of studies have examined the association between REM sleep parameters and clinical parameters. Tandon and associates (61) reported an inverse association between REM latency and negative symptoms. No association has been seen between sleep abnormalities and depressive symptoms (61), but two studies have shown that increased REM sleep may correlate with suicidal behavior in schizophrenia (67,68).

It is important to understand the longitudinal nature of

sleep abnormalities in schizophrenia, in order to elucidate their significance for pathophysiology. Stage 4 does not appear to improve while other sleep stages change following 3 to 4 weeks of conventional antipsychotic treatment (69). In a longitudinal study, alterations of SWS appeared to be stable when polysomnographic studies were repeated at 1 year, but the REM sleep parameters appeared to change. These observations suggest that SWS deficits in schizophrenia might be trait-related (70). Consistent with this view, delta sleep abnormalities have been found to correlate with negative symptoms (60) and with impaired outcome at 1 and at 2 years (71).

An association between attentional impairment and SWS deficits also has been reported in early studies (72). The thalamus plays a crucial role in attention and gating of information because it is the major relay station receiving input from the reticular activating system and limbic and cortical association areas. A defect in this structure could explain much of the psychopathology of schizophrenia and alterations in SWS.

Relation Between Sleep Findings and Neurobiology in Schizophrenia

Some clues to the possible pathophysiologic significance of SWS deficits in schizophrenia may derive from the studies of the ontogeny of sleep during normal adolescence, in the context of a neurodevelopmental framework for schizophrenia. Converging evidence suggests a substantial reorganization of human brain function during adolescence; a marked decline in synaptic density is seen in the postmortem prefrontal cortex during adolescence. Pronounced reductions in cortical gray matter volume and regional cerebral metabolism also have been seen during adolescence. Polysomnographic studies show major changes in EEG sleep patterns in adolescence; the amounts of SWS decrease (73) across the age span from childhood to late adolescence. The time courses for maturational changes in SWS, cortical metabolic rate, and synaptic density during the postnatal phase of human development are strikingly similar; Feinberg (74) suggested that cortical neurons, after birth, go through a phase of initial overproduction and subsequent regression (pruning) of neural elements. Thus, the maturational processes in sleep EEG, cortical synaptic density and regional cerebral metabolism might reflect a common underlying biological change (i.e., a large-scale synaptic elimination).

It is instructive to examine the polysomnographic abnormalities in schizophrenia in relation to the brain maturational parameters discussed in the preceding. In addition to SWS deficits, consistent alterations in structure and function of cortical and subcortical brain regions have been observed in schizophrenia. Cross sectional studies of the correlations between such alterations and sleep are valuable to better understand the pathophysiologic substrate of schizophrenia.

Altered Neuroanatomy

Reductions in cortical gray matter are seen in schizophrenia, perhaps more prominently in the frontal and temporal cortex as well as in thalamic volume (75). SWS generation appears to be regulated by a complex neural system involving the anterior brain regions and the thalamus. The relationship between alterations in these brain structures and SWS, therefore, is interesting. SWS tends to be inversely correlated with anterior horn ratio, a measure of frontal lobe size (76), and positively correlated with lateral ventricular volume (77). These observations may reflect reductions in subcortical structures such as the thalamus, which forms a substantial part of the ventricular boundaries. A correlation between thalamic volume and SWS deficits may be predicted, and is consistent with the former's critical role in generation of SWS.

Altered Neurochemistry

What are the neurochemical mechanisms involved in SWS deficits? SWS may result from several neurochemical processes that produce neural inhibition, functional differentiation, and EEG synchrony. Activation of the cholinergic system facilitates arousal and hastens REM sleep. Cholinergic hyperfunction postulated to underlie schizophrenia, therefore, could account for SWS and REM latency reduction in schizophrenia sleep (78). Interestingly, schizophrenic patients show supersensitive REM sleep induction with the cholinergic agonist R5 86 (79), suggesting cholinergic hyperfunction. Nicotinic receptors may also be involved; sensory gating deficits as evidenced by P50 event-related potentials, which are possibly related to central nicotinergic system alterations, are reversed following sleep in schizophrenia (80). Alternatively, serotonergic abnormalities may also be involved, as indicated by an inverse correlation between serotonin metabolites in the CSF and SWS in schizophrenia (81). Disturbances in catecholaminergic mechanisms may also underlie SWS deficits in schizophrenia. Norepinephrine, which is presumed to be hyperfunctional in schizophrenia, is inhibitory to REM; therefore, it may be argued that cholinergic and monoaminergic abnormalities mediate the constellation of reduced REM latency and SWS deficit without increases in REM sleep amounts in schizophrenia (78).

The possible relation between hormonal substances and delta sleep has also received some attention. Van Kammen and associates (82) showed an association between reduction in delta sleep induction peptide, a putative endogenous sleep modulator, and SWS decrements. Adenosine, an amino acid neuromodulator has drawn increasing interest in recent years as a possible endogenous sleep-promoting agent, as it tends to accumulate during waking hours (83). Adenosine agonists have been proposed as possible therapeutic agents in schizophrenia (84).

Altered Physiology

Some evidence, albeit modest, for decreased frontal lobe metabolism has been documented in schizophrenia using a variety of techniques, including PET, single photon emission computed tomography (SPECT), 31P MRS, and xenon 133 inhalation technique. It may be instructive to examine SWS deficits in the context of such physiologic alterations. An association has been demonstrated between SWS deficits and reduced frontal lobe membrane phospholipid metabolism as examined by 31P MRS (85).

Decreased synaptic density, postulated to underlie schizophrenia, could result in reduced SWS by decreased membrane surface (fewer dendrites per neuron), causing a smaller voltage response to the synchronizing stimulus. Recent studies in cats using single cell recordings (86) have shown that slower (<1 Hz) synchronized oscillations originate mainly in the neocortex, whereas delta waves (1 to 4 Hz) arise primarily from activity of thalamocortical neurons. A finer analysis of these oscillations may clarify the nature of pathophysiology in schizophrenia. Preliminary analysis of this question using period amplitude analyses suggested more prominent deficits in the <1 Hz range in schizophrenia, pointing to a thalamocortical dysfunction (64). This finding deserves further study and replication.

Effects of Antipsychotic Drugs on Sleep

Studies of the acute effects of neuroleptics have consistently shown improvements in sleep continuity, as reflected by reduced sleep latencies, improved sleep time, greater sleep efficiency, and prolongation of REM latency (58); however, changes in SWS have been less consistent. Studies that have examined the sedative effect of conventional neuroleptics have reported either no effects or modest increases in SWS. A recent study showed a robust increase in SWS with olanzapine following acute administration (87). On the other hand clozapine increases stage 2 sleep, but may actually decrease stage 4 sleep (88). These studies have frequently used small sample sizes; few studies have examined sleep variables in relation to acute versus long-term treatment with neuroleptics in a longitudinal design.

Attempts to examine polysomnographic characteristics of schizophrenia have to consider potential effects of neuroleptic discontinuation on sleep EEG. Neylan and associates (89) reported significant worsening of REM and non-REM sleep in a series of schizophrenic patients undergoing controlled neuroleptic discontinuation. Patients experiencing relapse has larger impairments in sleep. The effects of neuroleptic discontinuation continued to worsen from 2 to 4 weeks of a neuroleptic-free condition, and did not correlate with clinical change (90). These findings highlight the importance of controlling for medication state in investigation of EEG sleep in schizophrenia.

Future Directions

New knowledge on brain mechanisms of sleep is likely to open new avenues to investigate the pathophysiology of schizophrenia. First, functional brain imaging studies suggest distinct patterns of regional brain activation in SWS and REM sleep; such studies can provide clues to the pathophysiology of schizophrenia, especially used in conjunction with physiologic perturbation paradigms such as sleep deprivation (31). Second, sleep architecture changes dramatically during development; sleep studies during development in health and disease can shed considerable light on developmentally mediated neuropsychiatric disorders (91). Finally, sleep changes are often the earliest signs of disturbance, and may even represent trait-related vulnerability markers for psychiatric disorders; sleep studies of individuals at risk for schizophrenia are likely to be fruitful (92).

GERIATRIC DISORDERS

Late Life Depression

Assessments of the timing and quality of NREM and REM sleep cycles through EEG sleep studies have proven to be particularly useful indicators of homeostatic and adaptive physiologic processes during successful and pathologic aging in humans. In a study of healthy "old old" and "young old," Reynolds and colleagues (93) reported: (a) a small agedependent decrease in slow-wave sleep, in contrast to the stability of REM sleep measures from "young old" to "old old"; (b) much better preservation of slow wave sleep among aging women than men, particularly in the first NREM period of the night, but no sex-related differences in REM sleep measures; (c) greater stability of sleep maintenance among aging men than women; and (d) longer REM sleep latencies among aging women than men. In comparison with 20 year olds, 80 year olds have significant reductions in both REM sleep percent and latency, as well as a slower recovery from the effects of acute sleep loss. Elderly people show greater rigidity in sleep patterns, with less intersubject and intrasubject variability in habitual sleep times compared to the young (94); therefore, although some loss of REM and slow wave NREM sleep characterize the aging process, successful aging is associated with a relative stability of sleep states over the later years. One explanation for these findings may be some mild losses in both homeostatic as well as adaptive physiologic mechanisms that result in NREM and REM sleep decrements, respectively. Alternatively, information processing related to both homeostatic and adaptive behavior may be more stable and efficient in the elderly, especially in those for whom the aging process has been bridged successfully.

EEG sleep studies have also provided insights into the pathophysiology of disorders in which affective adaptation is significantly stressed in late-life, that is, in response to

significant losses or in acute depressive episodes. In a study of elderly volunteers who had lost a spouse, Reynolds and colleagues were able to distinguish EEG sleep changes discriminating subjects who did from those who did not develop an episode of major depression. Bereaved subjects with depression had significantly lower sleep efficiency, more early morning awakening, shorter REM latency, greater REM percent, and lower rates of delta-wave generation in the first NREM period, as compared to nondepressed bereaved volunteers. These findings are similar to those of elderly patients with recurrent unipolar depression. In a subsequent longitudinal study of bereaved elders who did not become clinically depressed, only increases in phasic REM activity and density (compared to normal controls) were observed throughout the first 2 years of bereavement (95). These findings are similar to those of Cartwright for depressed versus nondepressed divorcing women, suggesting that short REM latency and slow wave sleep are correlates of depression during stressful life events, whereas increased REM activity may correlate with successful recovery from stress in the absence of major depression. Given the selective activation of limbic and paralimbic structures during REM sleep, that is, structures related to affective adaptation, the increase in REM activity in the successful resolution of stressful events may relate to the activation of brain structures mediating adaptation to these stressful events. A failure to terminate this normal adaptive response, similar to the failure of counterregulatory neuroendocrine events in the generalized stress response, appears to result in a shift of central neurophysiologic events favoring cortical activation. This results in shifts away from homeostatic NREM sleep states, and toward more activated waking and REM sleep cortical states. In the EEG these are manifested by reductions in intrinsic, nonactivated thalamocortical synchronous EEG waves of NREM sleep, and an early entry into desynchronized REM sleep. Subjectively, this may relate to depressed patients complaints of both increased fatigue, or anergy (loss of homeostatic mechanisms) and increased internal "arousal" (shifting toward a more continuous on-line state of readiness to process salient stimuli).

Alzheimer's Disease

Disturbances in sleep commonly accompany Alzheimer's disease (AD) (96). These disturbances are a significant cause of distress for caregivers, often leading to institutionalization of these patients (97). The changes in sleep often parallel the changes in cognitive function in demented patients (98). Also, daytime agitation has been associated with sleep quality at night (99). A large-scale community based study of AD patients reported that sleeping more than usual and early morning awakenings were the most common sleep disturbances in noninstitutionalized patients. Nighttime awakenings, however, were more disturbing to caregivers.

Nighttime awakenings were associated with male gender, and greater memory and functional declines. Three groups of subjects were identified in association with nocturnal awakenings: (a) patients with only daytime inactivity; (b) patients with fearfulness, fidgeting, and occasional sadness; and (c) patients with multiple behavioral problems including frequent episodes of sadness, fearfulness, inactivity, fidgeting, and hallucinations.

In terms of sleep laboratory-based evaluations, sleep continuity disturbances in these patients include decreased sleep efficiencies, increased lighter stage 1 NREM sleep, and an increased frequency of arousals and awakenings. Sleep architecture abnormalities include decreases in stages 3 and 4 NREM sleep and some reports of decreases in REM sleep (100). Loss of sleep spindling and K complexes have also been noted in dementia. Sleep apnea has been observed in 33% to 53% of patients with probable AD (101). It is unclear if there is an increased prevalence of sleep apnea, however, in AD patients in relation to age- and gendermatched controls. Nocturnal behavioral disruptions, or "sundowning" are reported commonly in the clinical management of AD patients, although specific diagnostic criteria for a "sundowning" episode have been difficult to define (96,102). Despite extensive clinical research in this area, the pathophysiology of sundowning, including its relationship with brain mechanisms that control sleep/wake and circadian regulation remain unclear. Overall, the literature on sleep in AD suggest that the primary defect in this disease is the more general neurodegenerative changes that lead to the profound cognitive and functional declines of this disease and that the sleep changes are secondary manifestations of the disorder. If sleep is viewed as generated by core sleep systems that then require an intact neural structure throughout the rest of the brain for expression of behavioral states, then the sleep changes in AD are most likely related to end-organ failure as opposed to pathology in key sleep or circadian systems themselves.

Parkinson's Disease

Light, fragmented sleep occurs frequently in Parkinson's disease (PD) patients. Sleep problems have been reported in as many as 74% to 96% of patients (103). Complaints include frequent awakenings, early awakening, nocturnal craps, pains, nightmares, vivid dreams, visual hallucinations, vocalizations, somnambulisms impaired motor function during sleep, myoclonic jerks, excessive daytime sleepiness, REM sleep behavior disorder, and sleep-related violence leading to injury (103–106). These changes may result from the disease itself, or to complication from treatment with dopaminergic agents (103–105,107). Additionally, depression is common in PD and the sleep disruption may in part be related to this comorbid disorder (103).

Sleep architecture abnormalities include increased awakenings, reductions in stages 3 and 4 sleep, REM sleep, and sleep spindles (107,108). Reductions in REM latency have been observed. Increased muscular activity, contractions and periodic limb movements may prevent slow wave sleep and foster light fragmented sleep. Disorganized respiration also is found (109).

FUTURE DIRECTIONS

As one of the earlier tools available to psychiatric research for discovering the biological basis of mental disorders, EEG sleep recordings have been used extensively to characterize alterations in brain function across diverse mental disorders. This literature now forms the background for new research that can uncover the brain mechanisms that underlie these descriptive changes. Tools available for such purposes include refinements in electrophysiologic recordings using automated EEG and the concurrent use of electrical recordings of cognitive processes such as evoked responses to characterize changes in information processing during sleep in relation to mental disorders. Extensive advances in functional neuroimaging that are currently available, as well as in development, promise to provide us with dynamic images of brain function as it transitions throughout the sleep/wake cycle. In this manner, the functional neuroanatomic basis of the electrophysiologic abnormalities can be determined and interventions designed targeting not only specific neurotransmitter systems but systems that are specific to a discrete brain region that is responsible for the sleep/wake disturbance. The discovery of the genetic basis of narcolepsy brings the dream of uncovering the genetic basis of sleep disruption into closer view. Application of the advances in cognitive neuroscience to sleep also promise to define the importance of sleep in shaping cognitive function as well as the role of pathological sleep in disrupting waking cognitive activity.

ACKNOWLEDGMENTS

This work was supported in part by MH30915, MH52247, MH37869, MH00295, MH01414, MH45203, and the Theodore and Vada Stanley Foundation. The authors thank Robert Y. Moore for his contributions. EAN has received honoraria for speaking from Glaxo-Wellcome, Inc. MK has received research support from Pfizer Inc., Janssen Pharmaceutical Research Foundation, and Eli Lilly Pharmaceutical.

REFERENCES

- Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 1953;118:273–274.
- 2. Jouvet M. Recherches sur les structures nerveuses et les meca-

nismes responsables des differentes phases du sommeil physiologique. Arch Italiennes Biol 1962;100:125-206.

- Steriade M, Amzica F, Contreras D. Synchronization of fast (30 to 40 Hz) spontaneous cortical rhythms during brain activation. J Neurosci 1996;16:392–417.
- Nofzinger EA, Nichols TE, Meltzer CC, et al. Changes in forebrain function from waking to REM sleep in depression: preliminary analyses of [¹⁸F] FDG PET studies. *Psychiatry Res Neuroimag* 1999;91:59–78.
- Destexhe A, Contreras D, Steriade M. Cortically-induced coherence of a thalamic-generated oscillation. *Neuroscience* 1999; 92:427-443.
- Robbins TW, Everitt BJ. Arousal systems and attention. In: Gazzaniga M. *The cognitive neurosciences*. Cambridge: MIT Press, 1996:703-720.
- Moore RY, Abrahamson EA, van den Pol A. The hypocretin neuron system: an arousal system in the human brain. Arch Italiennes Biol 2001;139:195–205.
- 8. Steriade M, McCarley RW. Brainstem control of wakefulness and sleep. New York: Plenum Press, 1990.
- 9. Hobson JA, Pace-Schott E, Stickgold R. Dreaming and the brain: towards a cognitive neuroscience of conscious states. *Behav Brain Sci* 2000;23:793–842.
- Szymusiak R. Magnocellular nuclei of the basal forebrain: substrates of sleep and arousal regulation. *Sleep* 1995;18:478–500.
- Shiromani PJ, Scammell T, Sherin JE, et al. Hypothalamic regulation of sleep. In: Lydic R, Baghdoyan HA. *Handbook of behavioral state control: cellular and molecular mechanisms*. Boca Raton, FL: CRC Press, 1999:311–326.
- Edgar DM. Sleep-wake circadian rhythms and aging: potential etiologies and relevance to age-related changes in integrated physiological systems. *Neurobiol Aging* 1994;15:499–501.
- Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation [see comments]. *Cell* 1999;98:437–451.
- Nishino S, Ripley B, Overeem S, et al. Hypocretin (Orexin) deficiency in human narcolepsy [letter]. *Lancet* 2000;355: 39–40.
- McCarley RW, Hobson JA. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. *Science* 1975;189:58–60.
- Krueger JM, Obal F, Fang J. Humoral regulation of physiological sleep: cytokines and GHRH. J Sleep Res 1999;8:53–59.
- Semba K. The mesopontine cholinergic system: a dual role in REM sleep and wakefulness. In: Lydic R, Baghdoyan HA. *Handbook of behavioral state control: cellular and molecular mechanisms.* Boca Raton, FL: CRC Press, 1999:161–180.
- Luppi P-H, Peyron C, Rampon C, et al. Inhibitory mechanisms in the dorsal raphe nucleus and locus ceruleus during sleep. In: Lydic R, Baghdoyan HA. *Handbook of behavioral state control: cellular and molecular mechanisms*. Boca Raton, FL: CRC Press, 1999:195–212.
- Braun AR, Balkin TJ, Wesenten NJ, et al. Regional cerebral blood flow throughout the sleep-wake cycle. An H₂(¹⁵)O PET study. *Brain* 1997;120:1173–1197.
- Nofzinger EA, Mintun MA, Wiseman MB, et al. Forebrain activation in REM sleep: an FDG PET study. *Brain Res* 1997; 770:192–201.
- Calvo JM, Simon-Arceo K. Cholinergic enhancement of REM sleep from sites in the pons and amygdala. In: Lydic R, Baghdoyan HA. *Handbook of behavioral state control: cellular and molecular mechanisms.* Boca Raton, FL: CRC Press, 1999: 391–406.
- Sanford LD, Tejani-Butt SM, Ross RJ, et al. Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms. *Arch Italiennes Biol* 1995;134:81–99.

- 23. Buchsbaum MS, Gillin JC, Wu J, et al. Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. *Life Sci* 1989;45:1349–1356.
- Maquet P, Franck G. Cerebral glucose metabolism during the sleep-wake cycle in man as measured by positron emission tomography. In: Horne J. *Sleep '88*. New York: Gustav Fischer, 1989:76–78.
- 25. Clark C, Dupont R, Lehr P, et al. Is there a relationship between delta sleep at night and afternoon cerebral blood flow, assessed by HMPAO-SPECT in depressed patients and normal control subjects? Preliminary data. *Psychiatry Res* 1998;84:89–99.
- Maquet P, Degueldre C, Delfiore G, et al. Functional neuroanatomy of human slow wave sleep. J Neurosci 1997;17: 2807–2812.
- Hofle N, Paus T, Reutens D, et al. Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. *J Neurosci* 1997;15:4800–4808.
- Andersson JL, Onoe H, Hetta J, et al. Brain networks affected by synchronized sleep visualized by positron emission tomography. J Cereb Blood Flow Metab 1998;18:701–715.
- 29. Lydic R, Baghdoyan HA, Hibbard L, et al. Regional brain glucose metabolism is altered during rapid eye movement sleep in the cat: a preliminary study. *J Comp Neurol* 1991;304:517–529.
- Maquet P, Peters JM, Aerts J, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature* 1996; 383:163–166.
- Drummond SPA, Brown GC, Gillin JC, et al. Altered brain response to verbal learning following sleep deprivation. *Nature* 2000;43:655–657.
- Borbély AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195–204.
- Buzsaki G. Commentary: two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* 1989; 31:551-70.
- Llinas RR, Pare D. Commentary: of dreaming and wakefulness. *Neuroscience* 1991;44:521–535.
- Winson J. The biology and function of REM sleep. Curr Opin Neurobiol 1993;3:243–248.
- 36. Kavanau JL. Sleep and dynamic stabilization of neural circuitry: a review and synthesis. *Behav Brain Res* 1994;63:111–126.
- Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index (PSQI): a new instrument for psychiatric research and practice. *Psychiatry Res* 1989;28:193–213.
- Armitage R, Hoffmann RF, Rush AJ. Biological rhythm disturbance in depression: temporal coherence of ultradian sleep EEG rhythms. *Psychol Med* 1999;29:1435–1448.
- Nofzinger EA, Buysse DJ, Reynolds CF, et al. Sleep disorders related to another mental disorder (nonsubstance/primary): a DSM-IV literature review [Review]. J Clin Psychiatry 1993;54: 244–255; discussion 256–259.
- 40. Borbély AA, Tobler I, Loepfe M, et al. All-night spectral analysis of the sleep EEG in untreated depressives and normal controls. *Psychiatry Res* 1984;12:27–33.
- 41. Kupfer DJ, Frank E, McEachran AB, et al. Delta sleep ratio: a biological correlate of early recurrence in unipolar affective disorder. *Arch Gen Psychiatry* 1990;47:1100–1105.
- 42. Armitage R, Hoffmann R, Trivedi M, et al. Sleep macro- and microarchitecture in depression: age and gender effects. *Sleep Res* 1997;26:283.
- 43. Lauer CJ, Riemann D, Wiegand M, et al. From early to late adulthood changes in EEG sleep of depressed patients and healthy volunteers. *Biol Psychiatry* 1991;29:979–993.
- 44. Dahl RE, Ryan ND, Birmaher B, et al. EEG sleep measures in prepubertal depression. *Psychiatry Res* 1991;38:201–214.
- 45. Dew MA, Reynolds CF, Buysse DJ, et al. Electroencephalographic sleep profiles during depression. Effects of episode dura-

tion and other clinical and psychosocial factors in older adults. *Arch Gen Psychiatry* 1996;53:148–156.

- Rush AJ, Giles DE, Jarrett RB, et al. Reduced REM latency predicts response to tricyclic medication in depressed outpatients. *Biol Psychiatry* 1989;26:61–72.
- Giles DE, Jarrett RB, Roffwarg HP, et al. Reduced rapid eye movement latency: a predictor of recurrence in depression. *Neuropsychopharmacology* 1987;1:33–39.
- Sharpley AL, Walsh AE, Cowen PJ. Nefazodone—a novel antidepressant—may increase REM sleep. *Biol Psychiatry* 1992;31: 1070–1073.
- Nofzinger EA, Reynolds CF, Thase ME, et al. REM sleep enhancement by bupropion in depressed men. *Am J Psychiatry* 1995;152(2):274–276.
- Gillin JC, Sutton L, Ruiz C, et al. The cholinergic rapid eye movement test with arecoline in depression. *Arch Gen Psychiatry* 1991;48:264–270.
- Bhatti T, Gillin JC, Seifritz E, et al. Effects of a tryptophanfree amino acid drink challenge on normal human sleep electroencephalogram and mood. *Biol Psychiatry* 1998;43:52–59.
- 52. Gillin JC, Sohn JW, Stahl SM, et al. Ipsapirone, a 5-HT1A agonist, suppresses REM sleep equally in unmedicated depressed patients and normal controls. *Neuropsychopharmacology* 1996; 15:109–115.
- Ho AP, Gillin JC, Buchsbaum MS, et al. Brain glucose metabolism during non-rapid eye movement sleep in major depression: a positron emission tomography study. *Arch Gen Psychiatry* 1996;53:645–652.
- Nofzinger EA, Price JC, Meltzer CC, et al. Towards a neurobiology of dysfunctional arousal in depression: the relationship between beta EEG power and regional cerebral glucose metabolism during NREM sleep. *Psychiatry Res Neuroimag* 2000;98: 71–91.
- Wu J, Buchsbaum MS, Gillin JC, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry* 1999;156:1149–1158.
- 56. Clark CP, Gillin JC, Golshan S, et al. Polysomnography and depressive symptoms in primary alcoholics with and without a lifetime diagnosis of secondary depression and in patients with primary major depression. J Affect Disord 1999;52:177–185.
- Drummond SP, Gillin JC, Smith TL, et al. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. *Alcohol Clin Exp Res* 1998;22:1796–1802.
- Zarcone VP, Benson KL. Sleep and schizophrenia. Principles and practice of sleep medicine. Philadelphia: WB Saunders, 1994: 105–214.
- Benca RM, Obermeyer WH, Thisted RA, et al. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992; 49:651–668.
- Ganguli R, Reynolds CF, Kupfer DJ. Electroencephalographic sleep in young, never medicated schizophrenics. Arch Gen Psychiatry 1987;44:36–44.
- Tandon R, Shipley JE, Taylor S, et al. Electroencephalographic sleep abnormalities in schizophrenia: relationship to positive/ negative symptoms and prior neuroleptic treatment. Arch Gen Psychiatry 1992;49:185–194.
- Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in prefrontal cortex? The Feinberg hypothesis revisited. *J Psychiatric Res* 1994;28:239–265.
- Werth E, Achermann P, Borbely AA. Fronto-occipital EEG power gradients in human sleep. J Sleep Res 1997;6:102–112.
- 64. Keshavan MS, Reynolds CF, Miewald JM, et al. Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. *Arch Gen Psychiatry* 1998;55:443–448.
- 65. Benson KL, Sullivan EV, Lim KO, et al. The effect of total

sleep deprivation on slow wave recovery in schizophrenia. *Sleep Res* 1993;22:143.

- Horne J. Neuroscience. Images of lost sleep [News; Comment]. Nature 2000;403:605–606.
- Keshavan MS, Reynolds CF, Montrose D, et al. Sleep and suicidality in psychotic patients. *Acta Psychiatr Scand* 1994;89: 122–125.
- Lewis C, Tandon R, Shipley JR, et al. Biological predictors of suicidality in schizophrenia. *Acta Psychiatr Scand* 1996;94: 416–420.
- 69. Maixner S, Tandon R, Eiser A, et al. Effects of antipsychotic treatment on polysomnographic measures in schizophrenia: a replication and extension [Report]. *Am J Psychiatry* 1997;155: 1600–1602.
- Keshavan MS, Reynolds CF, Miewald JM, et al. A longitudinal study of EEG sleep in schizophrenia. *Psychiatry Res* 1996;59: 203–211.
- Keshavan MS, Reynolds CF, Miewald J, et al. Slow-wave sleep deficits and outcome in schizophrenia and schizoaffective disorder. *Acta Psychiatr Scand* 1995;91:289–292.
- Orzack MH, Hartman EL, Kornetsky C. The relationship between attention and slow wave sleep in schizophrenia. *Psychopharmacol Bull* 1977;13:59–61.
- 73. Smith JR, Karacan I, Yang M. Ontongeny of delta activity during human sleep. *Electroenceph Clin Neurophysiol* 1977;43: 229.
- Feinberg I. Schizophrenia: caused by a default in programmed synaptic elimination during adolescence. *J Psychiatric Res* 1982; 17:319–330.
- Andreasen NC, Arndt S, Swayze V, et al. Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science* 1994;266:294–298.
- Keshavan MS, Reynolds CF, Ganguli R, et al. Electroencephalographic sleep and cerebral morphology in functional psychoses: a preliminary study with computed tomography. *Psychiatry Res* 1991;39:293–301.
- Van Kammen DP, van Kammen WB, Peters J, et al. Decreased slow-wave sleep and enlarged lateral ventricles in schizophrenia. *Neuropsychopharmacology* 1988;1:265–271.
- Keshavan MS, Tandon R. Sleep abnormalities in schizophrenia: pathophysiologic significance. *Psychol Med* 1993;23:831–835.
- Riemann D. Cholinergic REM induction test: muscarinic supersensitivity underlies polysomnographic findings in both depression and schizophrenia. *J Psychiatric Res* 1994;28: 195–210.
- Griffith JM, O'Neill JE, Petty F, et al. Nicotinic receptor desensitization and sensory gating deficits in schizophrenia. *Biol Psychiatry* 1998;44:98–106.
- Benson KL, Faull KF, Zarcone VPJ. Evidence for the role of serotonin in the regulation of slow wave sleep in schizophrenia. *Sleep* 1991;14:133–139.
- Van Kammen DP, Widerlov E, Neylan TC, et al. Delta sleepinducing-peptide-like immunoreactivity (DSIP-LI) and sleep in schizophrenic volunteers. *Sleep* 1992;15:519–525.
- Porkka-Heiskanen T, Strecker RE, Thakkar M, et al. Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* 1997;276:1265–1268.
- Ferre S. Adenosine-dopamine interactions in the ventral striatum. Implications for the treatment of schizophrenia. *Psychopharmacol (Berl)* 1997;133:107–120.
- 85. Keshavan MS, Pettegrew JW, Reynolds CFJ, et al. Slow wave sleep deficits in schizophrenia: pathophysiologic significance. *Psychiatry Res* 1995;57:91–100.
- 86. Steriade M. Brain electrical activity and sensory processing during waking and sleep states. In: Kryger MH, Roth T, Dement

WC, eds. *Principles and practice of sleep medicine*. Philadelphia: WB Saunders, 1994:105–214.

- Salin-Pascual RJ, Herrera-Estrella M, Galicia-Polo L, et al. Olanzapine acute administration in schizophrenic patients increases delta sleep and sleep efficiency. *Biol Psychiatry* 1999;46: 141–143.
- Hinze-Selch D, Mullington J, Orth A, et al. Effects of clozapine on sleep: a longitudinal study. *Biol Psychiatry* 1997;42:260–266.
- Neylan TC, Van Kammen DP, Kelley ME, et al. Sleep in schizophrenic patients on and off haloperidol therapy: clinically stable vs. relapsed patients. *Arch Gen Psychiatry* 1992;49:643–649.
- Nofzinger EA, vanKammen DP, Gilbertson MW, et al. Electroencephalographic sleep in clinically stable schizophrenic patients: two- vs. six-weeks neuroleptic free. *Biol Psychiatry* 1993; 33:829–835.
- Dahl RE. The development and disorders of sleep. Adv Pediatr 1998;45:73–90.
- Lauer CJ, Schreiber W, Holsboer F, et al. In quest of identifying vulnerability markers for psychiatric disorders by all-night polysomnography. *Arch Gen Psychiatry* 1995;52:145–153.
- Reynolds CF, Monk TH, Hoch CC, et al. Electroencephalographic sleep in the healthy "old old": A comparison with the "young old" in visually scored and automated measures. *J Gerontol* 1991;46:M39–M46.
- 94. Monk TH, Reynolds CF, Machen MA, et al. Daily social rhythms in the elderly and their relation to objectively recorded sleep. *Sleep* 1992;15:322–329.
- Reynolds CF, Hoch CC, Buysse DJ, et al. *Sleep* after spousal bereavement: a study of recovery from stress. *Biol Psychiatry* 1993;34:791–797.
- Bliwise DL. Dementia. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*, second ed. Philadelphia: WB Saunders, 1994:790.
- Chenier MC. Review and analysis of caregiver burden and nursing home placement. *Geriatr Nurs* 1997;18:121–126.
- 98. Bliwise DL, Hughes M, McMahon PM, et al. Observed sleep/

wakefulness and severity of dementia in an Alzheimer's disease special care unit. *J Gerontol, Series A, Biol Sci Med Sci* 1995;50: M303–M306.

- Cohen-Mansfield J, Werner P, Freedman L. Sleep and agitation in agitated nursing home residents: an observational study. *Sleep* 1995;18:674–680.
- Prinz PN, Peskind ER, Vitaliano PP, et al. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. J Am Geriatr Soc 1982;30:86–93.
- Ancoli-Israel S, Klauber MR, Butters N, et al. Dementia in institutionalized elderly: relation to sleep apnea. J Am Geriatr Soc 1991;39:258–263.
- 102. Cohen-Mansfield J, Marx MS, Rosenthal AS. Dementia and agitation in nursing home residents: how are they related? *Psychol Aging* 1990;5:3–8.
- Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord* 1998;13:895–899.
- Factor SA, McAlarney T, Sanchez-Ramos JR, et al. Sleep disorders and sleep effect in Parkinson's disease. *Mov Disord* 1990; 5:280–285.
- Stocchi F, Barbato L, Nordera G, et al. Sleep disorders in Parkinson's disease. J Neurol 1998;245:S15–S18.
- Bernath O, Guilleminault C. Sleep-related violence, injury, and REM sleep behavior disorder in PD. *Neurology* 1999;52:1924.
- 107. Kales A, Ansel RD, Markham CH, et al. Sleep in patients with Parkinson's disease and normal subjects prior to and following levodopa administration. *Clin Pharmacol Therapeut* 1971;12: 397–406.
- Kostic VS, Susic V, Przedborski S, et al. Sleep EEG in depressed and nondepressed patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1991;3:176–179.
- Apps MC, Sheaff PC, Ingram DA, et al. Respiration and sleep in Parkinson's disease. J Neurol Neurosurg Psychiatry 1985;48: 1240–1245.

Neuropsychopharmacology: The Fifth Generation of Progress. Edited by Kenneth L. Davis, Dennis Charney, Joseph T. Coyle, and Charles Nemeroff. American College of Neuropsychopharmacology © 2002.