CHAPTER **15**

Neuroimaging in Sleep and Sleep Disorders

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Functional neuroimaging is a powerful tool to explore regional brain activity in humans. It includes a variety of metabolic and hemodynamic techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy. Neurophysiologic techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) are not reviewed here.

Neuroimaging in patients suffering from sleep disorders may serve several purposes. First, it can help characterize the cerebral consequences of sleep disruption due to intrinsic sleep disorders, or to extrinsic environmental or medical causes. For instance, neuroimaging studies have shown that chronic sleep fragmentation in sleep-disordered patients (e.g., patients with obstructive sleep apnea syndrome)[1] or acute sleep deprivation in normal subjects[2–4] eventually leads to impaired cognitive functioning associated with significant changes in the underlying pattern of regional brain activity.

Second, neuroimaging may serve to better characterize the pathogenic mechanisms of sleep disorders, or at least their cerebral correlates. This endeavor is hindered by the fact that, from the practical and methodologic points of view, scanning patients during their sleep is not easy. However, alternative approaches are available, as the functional and structural consequences of these sleep disorders can also be assessed during wakefulness. For instance, voxel-based morphometry analysis can be used to detect structural brain changes typical of specific sleep disorders. Likewise, cardiovascular regulation can be assessed by probing important reflexes, as during the Valsalva maneuver.

Third, neuroimaging might help to establish the nosography of sleep disorders. For instance, neuroimaging could help classify different subtypes of insomnia in terms of their underlying characteristic patterns of regional brain activity, an approach that may prove complementary to clinical observation.

Finally, functional neuroimaging can also be used to assess the effects of hypnotic drugs on regional brain function. This may enhance our understanding of their effects, assuming that hypnotic medications inducing typical patterns of brain activation rely on cellular mechanisms similar to those prevailing in normal sleep.

This chapter reviews attempts made in these various directions. To set the stage for the study of sleep disorders, we first describe recent contributions of neuroimaging techniques to the functional neuroanatomy of normal sleep in humans.

NEUROIMAGING IN NORMAL HUMAN SLEEP

Sleep profoundly impacts the activity of numerous physiologic systems (see, e.g., Kryger et al.[5]). PET, SPECT, or fMRI studies reviewed in this section have demonstrated that global and regional patterns of brain activity during sleep are remarkably different from those during wakefulness. These studies have also shown the persistence of brain responses to external stimuli during sleep, and plastic changes in brain activity related to previous waking experience.

Functional Neuroimaging of Normal Human Sleep

Noninvasive functional neuroimaging with PET brought an original description of the functional neuroanatomy of human sleep. These studies described a reproducible regional distribution of brain activity during sleep stages (rapid eye movement [REM] and non-REM [NREM] sleep) that largely differs from wakefulness, as expected from animal data. More recent data, using event-related fMRI, have also assessed the brain activity related to spontaneous neural events within sleep stages, such as sleep spindles.

NREM Sleep

In mammals, the neuronal activity observed during NREM sleep is sculpted by a cortical slow oscillation that alternates short bursts of firing ("up" states) and long periods of hyperpolarization ("down" states).[6] Slow oscillations organize the synchronization of other NREM sleep rhythms (spindles and delta waves),[7] and should also have a major impact on regional cerebral blood flow (rCBF), which when averaged over time decreases in the areas where they prevail. Taking into account that PET measurements average cerebral activity over 45–90 seconds, decreases in cerebral blood flow (CBF) and cerebral glucose metabolism during NREM sleep are thought to underlie a change in firing pattern, reflected by the slow oscillation and characterized by synchronized bursting activity followed by long hyperpolarization periods.[8] Accordingly, as compared to wakefulness, the average cerebral metabolism and global blood flow levels begin to decrease in light (stage 1 and stage 2) NREM sleep,[9–11] and reach their nadir in deep (stage 3 and 4) NREM sleep, also named slow-wave sleep (SWS).[12,13]

In animals, the cascade of events that generates NREM sleep oscillations among thalamo-neocortical networks is induced by a decreased firing in the activating structures of the brain stem tegmentum.[6] In agreement with animal data, humans PET studies show that brain stem blood flow is decreased during light NREM sleep[14] as well as during SWS.[14–17] During light NREM sleep, the pontine tegmentum appears specifically deactivated, whereas the mesencephalon seems to retain an activity that is not significantly different from wakefulness.[14] In SWS, both pontine and mesencephalic tegmenta are deactivated.[16]

The thalamus occupies a central position in the generation of NREM sleep rhythms, due to the intrinsic oscillating properties of its neurons and to the intrathalamic and thalamo-corticothalamic connectivity. As expected, in humans, regional activity decreases have been found in the thalamus during both light and deep NREM sleep in PET[14–16] and block-design fMRI[18] studies; rCBF decreases in the thalamus have also been evidenced in proportion to the power density of the EEG signal in the spindle and delta frequency range[19] (but see Dang-Vu et al.[20] for a critical discussion of these findings).

The role of the cortex in the generation of NREM sleep oscillations is equally important but not yet fully understood,[21] especially at the neuronal level. Electroencephalographic power density maps have revealed a relatively typical predominance of the delta frequency band in the frontal regions, whereas sigma power predominated over the vertex.[22] Human PET data similarly showed that the pattern of cortical deactivation was not homogeneously distributed throughout the cortex. As compared to wakefulness, the least active areas in SWS were observed in various associative cortices of the frontal (in particular in the dorsolateral and orbital prefrontal cortex) and parietal, and to a lesser extent in the temporal and insular, lobes.[14–16,23] In contrast, the primary cortices were the least deactivated cortical areas.[15] Finally, a meta-analysis of our own data[20] showed a linear (inverse) relationship between EEG spectral power within the delta frequency band and rCBF in ventromedial prefrontal regions during NREM sleep in non–sleep-deprived normal subjects. This result suggests an important role of medial prefrontal cortices in the modulation of delta waves.

The reasons for this heterogeneous cortical distribution remain unclear. One hypothesis is that, since polymodal association cortices are the most active cerebral areas during wakefulness, and because sleep intensity is homeostatically related to prior waking activity at the regional level,[24] these cortices might be more profoundly influenced by SWS rhythms than primary cortices.[8]

The predominance of rCBF decreases in prefrontal regions may be functionally important since these cortical regions are involved in mood regulation and in various cognitive functions (e.g., planning or probability matching)[25] that help adaptation of individual behaviors. Studies of the deleterious effects of sleep deprivation on human cognition also pointed to a high sensitivity of these association cortices to sleep deprivation (see later).

The previous functional brain imaging studies have compared periods or "blocks" of brain activity averaged over several tens of seconds or minutes between NREM sleep and wakefulness. Because hyperpolarization phases may predominate over these periods, the resulting picture emerging from these studies is decreasing brain activity during NREM sleep in the areas where slow oscillations are most prevalent. While NREM sleep is consistently characterized by a global and regional net decrease of brain activity over several seconds or minutes, the concept of NREM sleep as a stage of brain quiescence is not accurate, as we know from animal studies that NREM sleep is also characterized by transient bursts of neuronal discharge ("up" states) organized by NREM sleep oscillations. We conducted an event-related fMRI study during NREM sleep in normal non–sleep-deprived human volunteers and showed that the occurrence of the phasic sleep spindles was associated with increases of brain activity in a specific set of cortical and subcortical structures, including the thalamus, paralimbic areas, and superior

temporal gyri.[26] Moreover, beyond this general activation pattern, we also demonstrated that slow and fast spindles could be differentiated in terms of their macroscopic hemodynamic responses: slow spindles were specifically associated with activation of the superior temporal gyrus, and fast spindles preferentially recruited hippocampal and sensorimotor cortical areas. Besides bringing further evidence that spindles can be divided in two biologically distinct subtypes, this study demonstrates that NREM sleep cannot be reduced to a state of sustained brain deactivation but is characterized by phasic increases in brain activity triggered by NREM sleep oscillations, such as spindles, in agreement with animal data.

REM Sleep

REM sleep is characterized by desynchronized neuronal activity[27,28] and, correspondingly, by high cerebral energy requirements[12] and blood flow.[13,29] In this active but sleeping brain, some areas are particularly active, even more than during wakefulness, while others have lower than average regional activity.

PET studies have shown significant rCBF increases during REM sleep in the pontine tegmentum, thalamic nuclei, limbic and paralimbic areas, amygdaloid complexes,[30,31] hippocampal formation,[15,31] anterior cingulate cortex,[15,30,31] and orbitofrontal and insular cortices[31] (Fig. 15–1). Posterior cortices in temporo-occipital areas were also found to be activated,[15] although less consistently. In contrast, the inferior and middle dorsolateral prefrontal gyri, the inferior parietal cortex, and the posterior cingulate cortex and precuneus were the least active brain regions.[15,30]

Functional connectivity between remote brain areas is also modified during human REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory, is reversed during REM sleep.[15,32] Likewise, the functional relationship between the amygdala

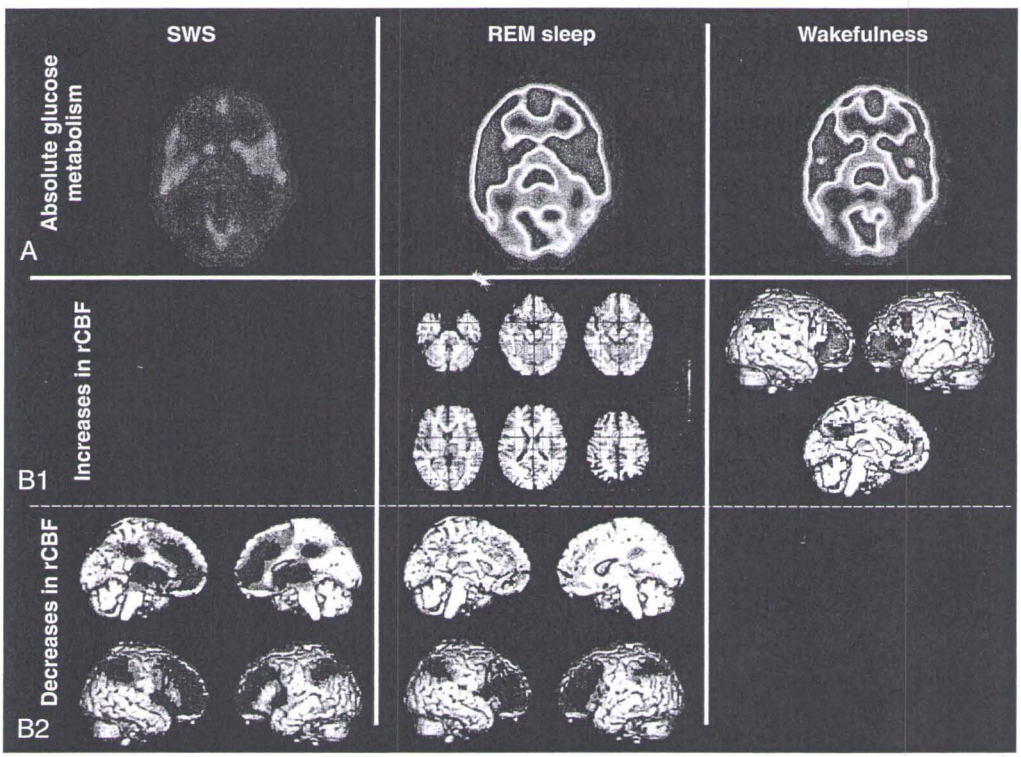

FIGURE 15–1 Cerebral glucose metabolism (CGM) and regional cerebral blood flow (CBF) during deep NREM sleep (*first column*), REM sleep (*second column*), and wakefulness (*third column*). **(Row A)** CGM quantified in the same individual at 1-week interval, using FDG and PET. The three images are displayed at the same brain level using the same color scale. The average CGM during deep NREM sleep (versus wakefulness) is significantly decreased. During REM sleep, the CGM is as high as during wakefulness. **(Row B1)** Distribution of the *highest* regional brain activity, as assessed by CBF measurement using PET, during wakefulness and REM sleep. The most active regions during *wakefulness* are located in the polymodal associative cortices in the prefrontal and parietal lobes (both on the medial wall and convexity). During *REM sleep,* the most active areas are located in the pontine tegmentum, thalami, amygdaloid complexes, and anterior cingulate cortex. Other data (not shown) have shown a large activity in the occipital cortices, insula, and hippocampus.[15] **(Row B2)** Distribution of the *lowest* regional brain activity, as assessed by CBF measurement using PET, during NREM and REM sleep. In both sleep stages, the least active regions are located in the polymodal associative cortices in the prefrontal and parietal lobes (convexity). During *NREM sleep,* the brain stem and thalami are also particularly deactivated. *See Color Plate*

and the temporal and occipital cortices is different during REM sleep than during wakefulness or NREM sleep.[33] This pattern suggests that functional interactions between neuronal populations are different during REM sleep than during wakefulness.

Regional brain activity in subcortical mesopontine and thalamic regions during human REM sleep[14,30,31] is in keeping with our current understanding of sleep generation in animals. REM sleep is generated by neuronal populations of the mesopontine reticular formation that monosynaptically activate the thalamic nuclei, which in turn activate the cortex.[27]

In contrast, the neurobiologic basis of the regional pattern of cortical activity during REM sleep remains unclear. Modifications of forebrain activity and responsiveness during REM sleep might rely on neuromodulatory changes. In cats, neurons in the raphe nuclei (serotonergic neurons) and locus ceruleus (noradrenergic cells) remain silent during REM sleep; simultaneously, mesopontine tegmentum cholinergic cells maintain a high firing rate.[27,34] To the best of our knowledge, there is still no report characterizing these neuromodulatory changes and their effect on regional brain function during human REM sleep.

Pontine waves, or ponto-geniculo-occipital (PGO) waves, are also primary features of REM sleep. In rats, the generator of the pontine waves projects to a set of brain areas shown to be active in human REM sleep: the occipital cortex, the entorhinal cortex, the hippocampus, and the amygdala as well as brain stem structures participating in the generation of REM sleep.[35] In cats, although most easily recorded in the pons,[36] the lateral geniculate bodies,[37] and the occipital cortex,[38] PGO waves are observed in many parts of the brain, including limbic areas (amygdala, hippocampus, cingulate gyrus).[39] Several observations suggest that PGO waves also occur during human sleep. In epileptic patients, direct intracerebral recordings in the striate cortex showed monophasic or diphasic potentials during REM sleep, isolated or in bursts.[40] In normal subjects, surface EEG revealed transient occipital and/or parietal potentials time-locked to the REMs.[41] Source dipoles of MEG signal were localized in the brain stem, thalamus, hippocampus, and occipital cortex during REM sleep.[42,43] Using PET, we showed that the rCBF in the lateral geniculate bodies and the occipital cortex is tightly coupled to spontaneous eye movements during REM sleep, but not during wakefulness.[44] This finding has been confirmed by an fMRI study.[45] Although fully conclusive components are still awaited, these various elements support the hypothesis that PGO-like activities participate in shaping the distribution of regional brain activity during human REM sleep.

Brain Reactivity to External Stimulation During Sleep

Electrophysiologic studies have demonstrated that sleep is not a state of complete unresponsiveness to external stimuli (see, e.g., Perrin et al.[46]). Early studies have shown that external stimuli can induce an autonomic or electrophysiologic response during human sleep, in particular after a relevant or meaningful stimulus presentation.[47] The analysis of event-related potential components could distinguish between different levels of external input processing during sleep. Middle-latency evoked potentials were found to be reduced during deep sleep, whereas brain stem auditory evoked potentials are not modulated by the vigilance state but rather by the circadian variations of body temperature.[48] As for long-latency components (P300), they are modulated by the sleep stage. During NREM sleep (and especially in stage 2 sleep), sensory stimulation triggers K complexes that are differentially affected by some stimulus features, with the later components of K complexes being more connected to the physical attributes of the stimulus and the early ones to its intrinsic significance.[49] In REM sleep, the evoked potential signs of stimulus discrimination differ from those observed during waking.[50] Indeed, words devoid of meaning were detected as anomalous and evoked N400 during waking, and yielded responses similar to those of congruous words in REM sleep.[50] Even if the information processing is quite comparable during stage 2 NREM and REM sleep (persistence of a differential response to the subject's own name, relative to any other proper name in both conditions), the electrophysiologic counterparts of these sleep phases show that their underpinning neural mechanisms are different.[48,50]

Available PET and fMRI data globally suggest that the processing of external stimuli can proceed beyond the primary cortices during NREM sleep. However, the mechanisms by which salient stimuli can recruit associative cerebral areas during sleep remain unclear. A pioneering fMRI study found that, during NREM sleep as during wakefulness, several areas continue to be activated by external auditory stimulation: the thalamic nuclei, the auditory cortices, and the caudate nucleus.[51] Moreover, the left amygdala and the left prefrontal cortex were found to be more activated by subjects' own names than by pure tones, suggesting the persistence during sleep of specific responses for meaningful or emotionally laden stimuli.

Other groups observed that auditory stimulation induced a decreased response in the auditory cortex and was related to negative signal in the visual cortex and precuneus.[52] Intriguingly, visual stimulation during SWS in adults elicited a decrease in activity in the occipital cortex.[53] This decrease was more rostral and dorsal compared to the relative rCBF increase along the calcarine sulcus found during visual stimulation in the awake state. The origin of this negative blood oxygenation level is still unclear despite recent replication.[54]

Sleep and Brain Plasticity

Evidence accumulates suggesting that sleep participates in the consolidation of recent memory traces.[55] Accordingly, PET studies have shown that waking experience influences

regional brain activity during subsequent REM and NREM sleep. Several brain areas, activated during procedural motor sequence learning (using a serial reaction time task) during wakefulness, have been found to be significantly more activated during subsequent REM sleep in subjects previously trained on the task than in nontrained subjects.[56] Furthermore, this effect is not observed in subjects trained to a task with similar practice requirements but devoid of any sequential content.[57] These findings speak against use-dependent changes in regional brain activations. Additionally, functional coupling between learning-related areas was found to be enhanced during post-training REM sleep.[58] Another PET study demonstrated that hippocampal and parahippocampal areas, which are activated during a spatial memory task, can be reactivated during post-training NREM sleep and that the amount of hippocampal activity during SWS positively correlated with overnight improvement in the memory for spatial locations.[59] Collectively, these findings suggest that reactivations of regional activity and modifications of functional connectivity during post-training sleep reflect the off-line processing of recent memory, which eventually leads to improved performance the next day. Moreover, these results are in line with behavioral data suggesting that NREM sleep and REM sleep differentially modulate the consolidation of declarative and nondeclarative memories, respectively.[60,61] However, they do not rule out an alternative hypothesis that natural succession of NREM sleep and REM sleep is also mandatory for memory consolidation. Additionally, these results are consistent with a recent intracranial EEG study in epileptic patients showing that, during sleep, functional connectivity between rhinal and hippocampal structures was larger for patients with good dream recall than for those with poor recall after they were awaked during REM sleep.[62]

Finally, recent fMRI studies demonstrated that sleep deprivation hinders the plastic changes that normally would occur during post-training sleep.[63] In this study, the effects of normal sleep or sleep deprivation on learning-dependent changes in regional brain activity were assessed after the subjects were trained on a pursuit task, in which they had to hold a joystick position as close as possible to a moving target, whose trajectory was predictable on the horizontal axis but not on the vertical axis. The time on target was used as the behavioral performance parameter. In the first group, subjects were totally sleep-deprived during the first post-training night, while in the second group, they were allowed to sleep. Both groups were then retested after 2 more nights of normal sleep in order to recover a similar state of arousal across the two groups and between the training and retest sessions. The fMRI scanning session was recorded during the retest, while subjects were exposed to the previously learned trajectory and also to a new one in which the predictable axis was vertical. Behavioral results showed that the time on target was larger for the learned trajectory than for the new one in both groups during the retest, and that this performance gain was greater in the sleeping group than in the sleep deprivation group. The fMRI data showed a significant effect of learning, irrespective of the group, in two regions: the left supplementary eye field and the right dentate nucleus. A region of the right superior temporal sulcus, close to regions coding for motion processing (biologic motion, smooth pursuit, etc.), was found to be more active for the learned than for the new trajectory, and more so in the sleeping group than in the sleep deprivation group. The functional connectivity also showed that the dentate nucleus was more closely linked to the superior temporal sulcus, and the supplementary eye field to the frontal eye field, for the learned than for the new trajectory, and more so in the sleeping group. Moreover, interactions between the temporal cortex and cerebellum, as well as between the frontal eye field and the supplementary eye field, are both known to be implicated in the standard pursuit eye movement pathways.[64] These results therefore suggest that the performance on the pursuit task relies on the subject's ability to learn the motion characteristics of trajectory in order to program optimal motor pursuit execution. Sleep deprivation during the first post-training night would disturb the slow processes that lead to the acquisition of this procedural skill and alter related changes in functional connectivity that were reinforced in subjects allowed to sleep.[63]

Recently, Orban et al.[65] used fMRI in order to map regional cerebral activity during place-finding navigation in a virtual town, immediately after learning and 3 days later, in subjects either allowed regular sleep (RS) or totally sleep-deprived (SD) on the first post-training night. Results showed that, at immediate and delayed retrieval, place-finding navigation elicited increased brain activity in an extended hippocampo-neocortical network in both RS and SD subjects. Moreover, behavioral performance was equivalent between groups. However, striatal navigation-related activity increased more at delayed retrieval in RS than in SD subjects. Furthermore, correlations between striatal response and behavioral performance, as well as functional connectivity between the striatum and the hippocampus, were modulated by post-training sleep. Overall, these data suggest that brain activity is restructured during sleep in such a way that navigation in the virtual environment, initially related to a hippocampus-dependent spatial strategy, becomes progressively contingent in part on a response-based strategy mediated by the striatum. Interestingly, both neural strategies eventually relate to equivalent performance levels, indicating that covert reorganization of brain patterns underlying navigation after sleep is not necessarily accompanied by overt changes in behavior.[65] Further studies have also evidenced a reorganization of brain activity when post-training sleep is allowed both for neutral[66] and emotional[67] verbal material. In addition, exposure to

an odor during SWS that had been presented as context during prior learning improved the retention of hippocampus-dependent declarative memories and elicited a significant hippocampal activation during SWS.[68]

In addition, EEG and MEG studies have provided robust evidence for the "sleep and memory consolidation" hypothesis by focusing on more specific sleep features and mechanisms that are regarded as important for different types of memory, including sleep spindles,[69–72] slow waves,[73] or the actual number of rapid eye movements.[74] For instance, sleep homeostasis has a local synaptic component, which can be triggered by a learning task involving specific brain regions. The local increase in slow-wave activity after learning correlated with improved performance of the task after sleep.[73] Moreover, the induction of slow oscillation–like potential fields by transcranial application of slowly oscillating potentials (0.75 Hz) during early nocturnal NREM sleep (i.e., a period of emerging SWS) enhanced the retention of hippocampus-dependent declarative memories in healthy humans. This kind of stimulation induced an immediate increase in SWS, endogenous cortical slow oscillations, and slow spindle activity in the frontal cortex.[75] Last but not least, it has been suggested that sleep may promote "creativity" or "insight".[76,77]

Alertness, Performance, and Sleep Deprivation

Sleep deprivation or fragmentation is increasingly common in industrialized societies (noisy environments, shift work). Likewise, many sleep disorders tend to become more frequent (e.g., insomnia, anxiety disorders). The considerable proportion of vehicle accidents related to sleep loss is now viewed as a serious concern for public health.[78] The impact of sleep deprivation on cognition and brain functions has been assessed mainly in healthy subjects. By comparison, studies on the consequences of sleep disorders on behavior and cerebral activity remain scarce.

Basal Metabolism

An early study investigated the effect of total sleep deprivation (about 32 hours) on brain metabolism.[79] Although global brain metabolism was not affected by sleep deprivation, absolute regional glucose metabolism significantly decreased in the thalamus, basal ganglia, and cerebellum. A significant reorganization of regional activity was observed after sleep deprivation, with relative decreases in the cerebral metabolic rate of glucose (CMRglu) within the temporal lobes and relative increases in the visual cortex.[79] Additionally, sleep deprivation significantly reduced performance in an attentional continuous performance test, and this decrease was significantly correlated with reduced metabolic rate in thalamic, basal ganglia, and limbic regions.[79]

Cognitive Challenges

Sleep deprivation is known to alter alertness and performance in a series of cognitive tasks. Several neuroimaging studies have tried to determine the underlying patterns of cerebral activity during different cognitive tasks. The cerebral responses to sleep deprivation seem to depend on the type of task and also on its level of difficulty. Both decreases and increases in responses were reported. The former were interpreted as metabolic impairments related to sleep deprivation, whereas the latter were viewed as compensatory responses.

A recent study showed that, even after as little as 24 hours of continuous wakefulness, significant decreases in global CMRglu are observed with [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG) PET.[3] When subjects performed a sleep deprivation–sensitive serial addition/subtraction task (which combines arithmetic processing and working memory), significant decreases in absolute regional CMRglu were found in several cortical and subcortical structures, whereas no areas of the brain showed any significant increase in regional metabolism. Alertness and cognitive performance scores declined in parallel with deactivations in the thalamus and in the prefrontal and posterior parietal cortices.[3]

The same group of researchers characterized the cerebral effects of 24, 48, and 72 hours of sleep deprivation during the same task performance in 17 healthy subjects using correlations with performance measures outside of the scanner and metabolism during resting state assessed by ^{18}FDG PET.[4] Results showed that absolute CMRglu and relative regional CMRglu (rCMRglu) decreased further at 48 and 72 hours of sleep deprivation primarily in the prefrontal and parietal cortices and in the thalamus, the same areas that showed decreases at 24 hours of sleep deprivation. The authors proposed that the decreases in CMRglu induced in the prefrontal-thalamic network by sleep deprivation underlie the progressive impairment in cognitive performance and alertness and the progression toward sleep onset. In contrast, increased activity in visual and motor areas would reflect voluntary attempts to remain awake and perform despite a continuing decline in prefrontal-thalamic network activity.[4]

In these CMRglu studies, metabolism during resting state was correlated with performance measures obtained outside of the scanner. However, a different picture emerges when subjects are scanned during task performance.

Drummond and colleagues used fMRI on normal subjects while those subjects performed different cognitive tasks after a normal night of sleep or following 35 hours of sleep deprivation. In a first report,[2] the study used a serial subtraction task. Bilateral activations in the prefrontal, parietal, and premotor cortices were found during task practice after a normal night of sleep, whereas activity in these regions declined markedly after sleep

deprivation, mainly in the prefrontal cortex,[2] which is in agreement with the hypothesis of prefrontal cortex vulnerability to sleep deprivation.[80] Likewise, Mu and colleagues[81] found reduced activations in several frontal and parietal regions (left dorsolateral prefrontal cortex, right ventrolateral prefrontal cortex, supplementary motor area, Broca's area, bilateral posterior parietal cortices) but no significant increased activations during practice of the Sternberg working memory task (SWMT) after 30 hours of sleep deprivation compared to normal sleep. However, a very different pattern emerged when using other types of tasks. For example, the effects of 35 hours of continuous wakefulness on cerebral activation during verbal learning (memorizing a list of words) was also investigated using fMRI.[82] The authors found that the prefrontal cortex and parietal lobes were more activated during verbal learning after 1 night of sleep deprivation than after normal sleep. In addition, increased subjective sleepiness in sleep-deprived subjects correlated significantly with the amount of prefrontal cortex activation, while stronger parietal lobe activation was linked to less impairment in the free recall of words. It has been suggested that these results reflect dynamic, compensatory changes in cerebral activation during verbal learning after sleep deprivation.[82] Likewise, another study found stronger correlation between difficulty in a logical reasoning task and increased activity in the bilateral inferior parietal lobes, bilateral temporal cortex, and left inferior and dorsolateral prefrontal cortex following 35 hours of continuous wakefulness than after normal sleep.[83] This suggests that compensatory mechanisms may lead to activation in regions that do not show significant responses to task demands in the well-rested condition, as well as to stronger responses within regions typically underlying task performance.[83]

Neurobehavioral (fMRI) effects of 24 hours of continuous wakefulness were assessed using two verbal working memory tasks of different difficulty levels, known to induce responses in frontal-parietal networks in normal, non–sleep-deprived conditions. After sleep deprivation, activity was reduced in the medial parietal, anterior medial frontal, and posterior cingulate regions in both tasks, and disproportionately greater activation of the left dorsolateral prefrontal cortex and bilateral thalamus was observed when additional manipulation of information in working memory was required[84] (see also Choo et al.[85]).

Other cognitive domains seem to be impaired by sleep deprivation. For instance, competent decision making was impaired after sleep deprivation, which induced a modulation of activation in the nucleus accumbens and insula, brain regions associated with risky decision making and emotional processing.[86]

These data suggest that decreases in regional brain activity could contribute to cognitive impairment after sleep deprivation and that increased prefrontal and thalamic activation may represent compensatory adaptation. In a similar attempt to better understand how sleep deprivation might interact with task difficulty, the effects of normal sleep and 36 hours of total sleep deprivation were assessed by fMRI during a verbal learning task with two levels of difficulty (easy and difficult words).[87] A set of regions showed increased response to difficult words after sleep deprivation compared with normal sleep (inferior frontal gyrus, dorsolateral prefrontal cortex and inferior parietal lobe, bilaterally). While better free recall performance on the difficult words following sleep deprivation was positively related to activation within the left inferior and superior parietal lobes and left inferior frontal gyrus, it was negatively related to activation within the right inferior frontal gyrus. Consequently, the performance relationships are thought to be both beneficial (as a compensatory function) and deleterious (as an interference with task performance), depending on the brain regions implicated.

Since prefrontal cortex functioning appears to be affected by sleep loss, processes mediated by this region should be altered after sleep deprivation (e.g., attention, emotion, motivation, feeding, olfaction). In order to asses the effects of sleep deprivation on olfaction, which is mediated by the orbitofrontal cortex, a region known to have decreased activity after sleep deprivation,[3] Killgore and McBride[88] studied 38 healthy subjects at rest and after 24 hours of sleep deprivation. Relative to rested baseline performance, sleep-deprived subjects showed a significant decline in the ability to identify specific odors on the Smell Identification Test.

Duration of Sleep Deprivation

Chronic restriction of sleep to 6 hours or less per night produces cognitive impairments similar to up to 2 nights of total sleep deprivation. Thus, it appears that moderate sleep restriction can seriously impair waking neurobehavioral functions in healthy adults, who are very often unaware of such deficits.[89] Sleep debt could be better understood as a consequence of extended wakefulness, with a neurobiologic "cost" that could accumulate over time.[89] However, rapid sleep loss has been shown to produce significantly more impairment on tests of alertness, memory, and performance compared to the slow accumulation of a comparable amount of sleep loss.[90] Some authors have proposed that this may reflect some mechanism(s) of adaptation to chronic sleep deprivation.[90] While the majority of the neuroimaging studies on sleep deprivation have used 1 night of sleep deprivation (24 hours of continuous wakefulness), neuroimaging studies that systematically assess what happens following shorter or longer sleep deprivation duration are still awaited.[4]

Personal Vulnerability to Sleep Deprivation

People may be differently affected by the same sleep-depriving environmental conditions. Results from one study suggest that brain responses to sleep deprivation for a given task are modulated by individual vulnerability

to sleep deprivation.[91] In this study, subjects were divided into two groups, a sleep deprivation (SD)–resilient group and an SD-vulnerable group, according to their performance on the SWMT after sleep deprivation. In the SD-resilient group, significant activations were found in several cortical areas (left dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex, left supplementary motor area, left posterior parietal cortex) during practice of the SWMT after sleep deprivation. By contrast, in the SD-vulnerable group, only the left dorsolateral prefrontal cortex was found to be activated after sleep deprivation. The patterns of brain activation after sleep deprivation may therefore differ as a function of the subjects' individual vulnerability to sleep deprivation.[91] The same group conducted another fMRI study on fatigue vulnerability in military pilots. Pilots were scanned during the SWMT under non–sleep-deprived conditions and individual fatigue vulnerability was quantified using performance on a flight simulation during 37 hours of continuous wakefulness. Correlation analyses revealed that global cortical activation was significantly related to fatigue vulnerability on flight-simulator performance. The authors therefore proposed that baseline fMRI scan activation during the SWMT may provide a good index of individual fatigue susceptibility.[92]

Recently, interindividual differences in working memory performance were evaluated in 26 healthy subjects both after normal sleep and after 24 and 35 hours of sleep deprivation using fMRI.[93] In both sleep deprivation sessions, there was reduced task-related activation in the superior parietal regions and left thalamus, as compared to normal sleep. Moreover, activation of the left parietal and left frontal regions after normal sleep was negatively correlated with individual performance decline from normal sleep to 24 hours of sleep deprivation. Thus, frontoparietal activation after normal sleep could differentiate individuals who will maintain working memory performance following sleep deprivation from those who will be vulnerable to its effects.

In another study, individuals better able to maintain inhibitory efficiency in a go/no-go task after sleep deprivation could be distinguished by lower stop-related, phasic activation of the right ventral prefrontal cortex during rested wakefulness.[94] These individuals also showed a larger rise in such activation both in that region and in the right insula after sleep deprivation relative to people whose inhibitory efficiency declined.

Interestingly, the most robust behavioral marker of vulnerability to sleep deprivation was the change in the intraindividual variability of reaction times. This was shown both to be stable over time and to be correlated with the drop in left parietal activation from rested wakefulness to sleep deprivation.[95] The modulation of this parietal activation may provide a good physiologic marker of vulnerability to sleep deprivation because of its reproducibility.

Functional Imaging and Drug Response

Functional neuroimaging can also be used to explore the effect of drugs on brain function and vigilance states and the influence of several neurotransmitter systems in the regulation of human sleep. Several examples are available in studies on assessment of muscarinic cholinergic receptors[96] and modafinil[97] in narcolepsy, use of bupropion in depression,[98] and assessment of opioid receptor agonists in restless legs syndrome.[99]

Several studies assessed the effects of benzodiazepines and sedative-hypnotics on brain function.[100–104] For instance, lorazepam administration markedly decreases regional brain glucose metabolism in the thalamus and occipital cortex during wakefulness.[100] It was suggested that benzodiazepine-induced changes in thalamic activity may account for the sedative properties of these drugs, since changes in metabolic activity in the thalamus correlated to lorazepam-induced sleepiness. During sleep induced by zolpidem (an imidazopyridine hypnotic relatively selective for the BZ1 or omega receptor), rCBF was found to decrease in the anterior cingulate cortex during REM sleep while it decreased in the prefrontal cortex and the insula during NREM sleep.[103] Finally, blood flow decreased in the basal forebrain and amygdaloid complexes during NREM sleep induced by triazolam (a short-acting benzodiazepine).[105] These results suggest that hypnotic effects of the benzodiazepines may be mediated mainly by deactivation of forebrain control systems that are usually strongly activated during active wakefulness, and also by the anxiolytic effect induced by deactivation of the amygdaloid complexes.[105]

NEUROIMAGING IN SLEEP DISORDERS

Sleep may be disrupted in a number of conditions ranging from medical diseases (e.g., endocrine disorders, chronic pain, brain lesions, sleep apnea) and psychiatric disorders (e.g., anxiety, depression, schizophrenia) to environmental situations (e.g., jet lag, shift work, noisy environment).

In this section, we consider several primary sleep disorders (narcolepsy, periodic limb movement disorder, idiopathic insomnia, recurrent hypersomnia, and obstructive sleep apnea) as well as specific parasomnia syndromes (sleepwalking, REM sleep behavior disorder) and several sleep disorders associated with psychiatric or neurologic disorders (psychoses, mood disorders, fatal familial insomnia, Landau-Kleffner syndrome and related disorders). We do not review sleep disorders due to disturbances from external, environmental sources.

Idiopathic Insomnia

Idiopathic insomnia is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality in the neurologic control of sleep-wake regulation systems.[106] This disorder is thought to reflect an imbalance between

the arousal system and the various sleep-inducing and sleep-maintaining systems. Neuroanatomic, neurophysiologic, or neurochemical dysfunctions or lesions within the sleep-wake systems are suspected in some of these patients.[106]

Theoretically, either hyperactivity within the arousal system or hypoactivity within the sleep system may cause idiopathic insomnia, but hyperarousal is believed to be the final common pathway of the disorder.[106] Increased arousal might be of a physiologic, cognitive, or affective nature; it is likely that these categories overlap,[5,107] since several studies have reported increased alertness on the Multiple Sleep Latency Test, increased heart rate during the sleep period, increased anxiety on rating scales, and increased tension during wakefulness.[107–109] In addition, poor sleep leads to altered mood and motivation, decreased attention and vigilance, low levels of energy and concentration, and increased daytime fatigue.[106]

Quantitative EEG recordings suggest an overall cortical hyperarousal in insomnia. However, hyperarousal in primary insomnia was also found to be associated with greater increase in beta/gamma activity at sleep onset, followed by a decline of high-frequency EEG activity leading to a period of hypoarousal.[110] This could explain why some neuroimaging studies showed a cortical hyperarousal pattern in insomnia while others reported a decrease in cortical functions. In the latter case, decreased metabolism might originate from time-window coincidence of the cortical hypoarousal period to neuroimaging acquisition, and therefore does not discard the hyperaousal hypothesis of primary insomnia.

Only a few studies tried to characterize the functional neuroanatomy of idiopathic insomnia disorder (referred to as primary insomnia in these reports). rCBF was estimated using technetium-99m–labeled hexamethylene-propyleneamine oxime (^{99m}Tc-HMPAO), a gamma-emitting radionuclide imaging agent used in the evaluation of rCBF, in five insomniacs and four normal sleepers. Patients with insomnia showed major rCBF decrease in the basal ganglia, medial frontal cortex, occipital cortex, and parietal cortex. These results suggest that idiopathic insomnia is associated with an abnormal pattern of regional brain activity during NREM sleep that particularly involves a dysfunction in the basal ganglia.[111]

More recently, ^{18}FDG PET was used to measure regional CMRglu of 7 patients with idiopathic insomnia and 20 healthy age- and gender-matched subjects during waking and NREM sleep.[112] Insomniac patients showed increased global CMRglu during sleep as compared to healthy subjects, suggesting an overall cortical hyperarousal in insomnia. Moreover, insomniac patients had a smaller decline, related to healthy subjects, in relative CMRglu from waking to sleep states in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices (Fig. 15–2). During wakefulness, reduced relative metabolism, as compared to healthy subjects, was found in the prefrontal cortex bilaterally, in the left temporal, parietal, and occipital cortices, and in the thalamus, hypothalamus, and brain stem reticular formation. These findings confirm that regional brain activity does not normally progress from waking to sleep states in patients with insomnia. Additionally, it was proposed that daytime fatigue resulting from inefficient sleep may be reflected by decreased activity in the prefrontal cortex.[112]

Four of the insomnia patients from the Smith et al. study were rescanned after they had been treated with cognitive behavioral therapy.[113] After this psychotherapeutic

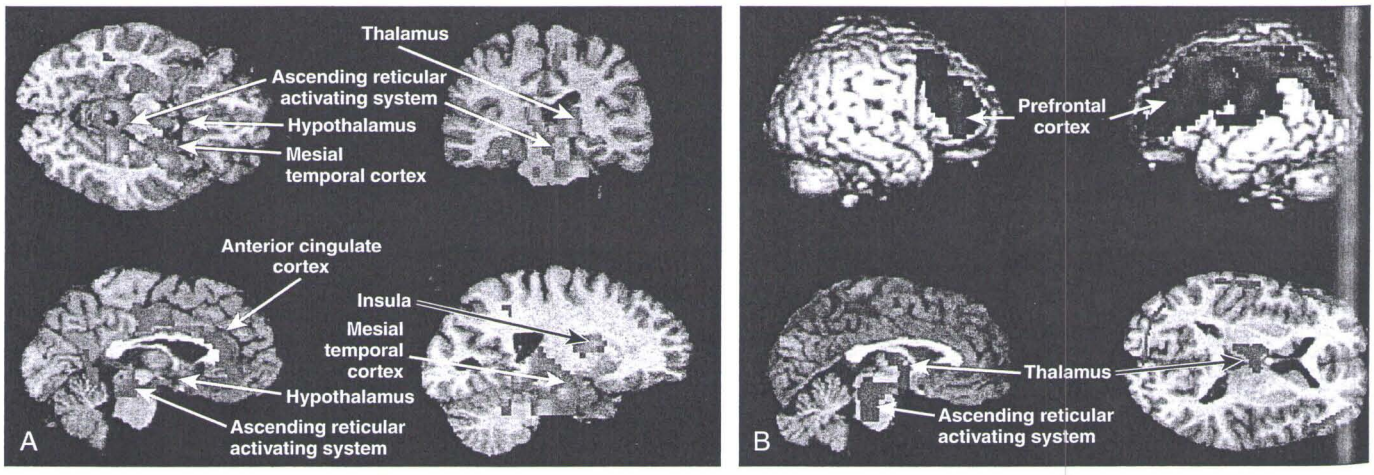

FIGURE 15–2 CMRglu assessed by ^{18}FDG PET in insomniacs (versus healthy subjects) during waking and NREM sleep. **(A)** Brain structures that did not show decreased cerebral metabolic rate of glucose (CMRglu) from waking to sleep states in patients with idiopathic insomnia. **(B)** Brain structures where relative metabolism while awake was higher in healthy subjects than in patients with insomnia. Differences in all regions shown reached statistical significance ($p < 0.05$), corrected at the cluster level. *(Reproduced with permission from Nofzinger EA, Buysse DJ, Germain A, et al: Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161:2126. Copyright 2004, American Psychiatric Association.) See Color Plate*

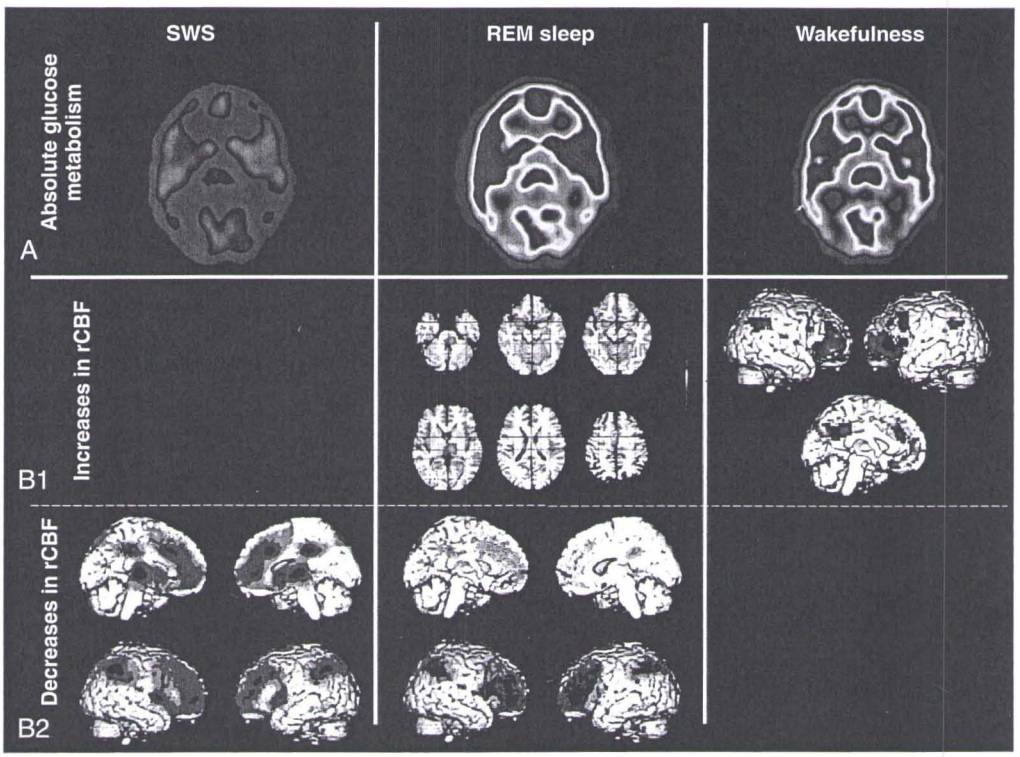

FIGURE 15–1 Cerebral glucose metabolism (CGM) and regional cerebral blood flow (CBF) during deep NREM sleep (*first column*), REM sleep (*second column*), and wakefulness (*third column*). **(Row A)** CGM quantified in the same individual at 1-week interval, using FDG and PET. The three images are displayed at the same brain level using the same color scale. The average CGM during deep NREM sleep (versus wakefulness) is significantly decreased. During REM sleep, the CGM is as high as during wakefulness. **(Row B1)** Distribution of the *highest* regional brain activity, as assessed by CBF measurement using PET, during wakefulness and REM sleep. The most active regions during *wakefulness* are located in the polymodal associative cortices in the prefrontal and parietal lobes (both on the medial wall and convexity). During *REM sleep,* the most active areas are located in the pontine tegmentum, thalami, amygdaloid complexes, and anterior cingulate cortex. Other data (not shown) have shown a large activity in the occipital cortices, insula, and hippocampus.[15] **(Row B2)** Distribution of the *lowest* regional brain activity, as assessed by CBF measurement using PET, during NREM and REM sleep. In both sleep stages, the least active regions are located in the polymodal associative cortices in the prefrontal and parietal lobes (convexity). During *NREM sleep,* the brain stem and thalami are also particularly deactivated. (See page 200)

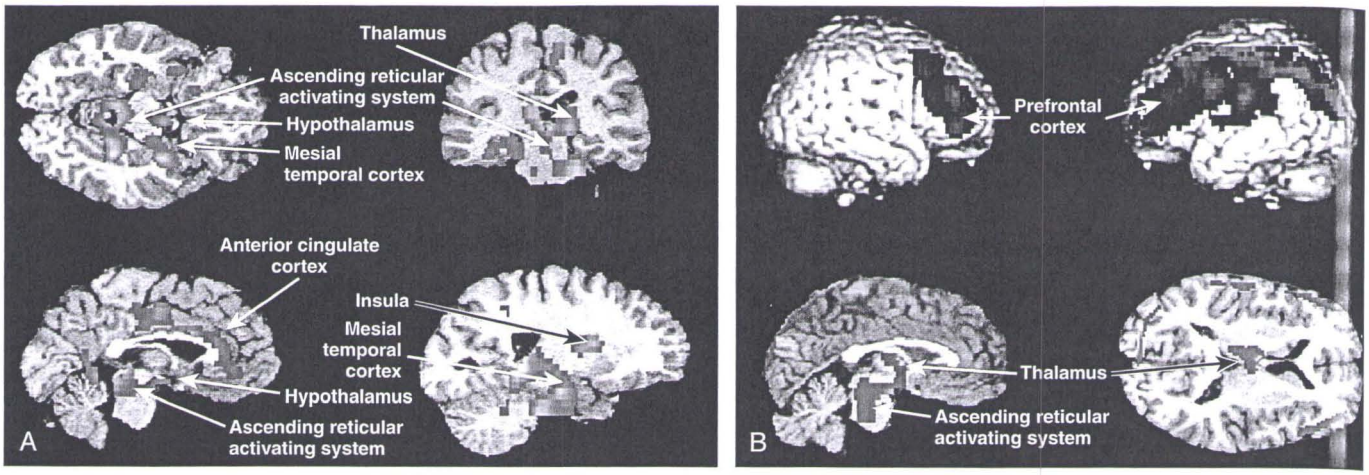

FIGURE 15–2 CMRglu assessed by ^{18}FDG PET in insomniacs (versus heathy subjects) during waking and NREM sleep. **(A)** Brain structures that did not show decreased cerebral metabolic rate of glucose (CMRglu) from waking to sleep states in patients with idiopathic insomnia. **(B)** Brain structures where relative metabolism while awake was higher in healthy subjects than in patients with insomnia. Differences in all regions shown reached statistical significance ($p < 0.05$), corrected at the cluster level. *(Reproduced with permission from Nofzinger EA, Buysse DJ, Germain A, et al: Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161:2126. Copyright 2004, American Psychiatric Association.)* (See page 206)

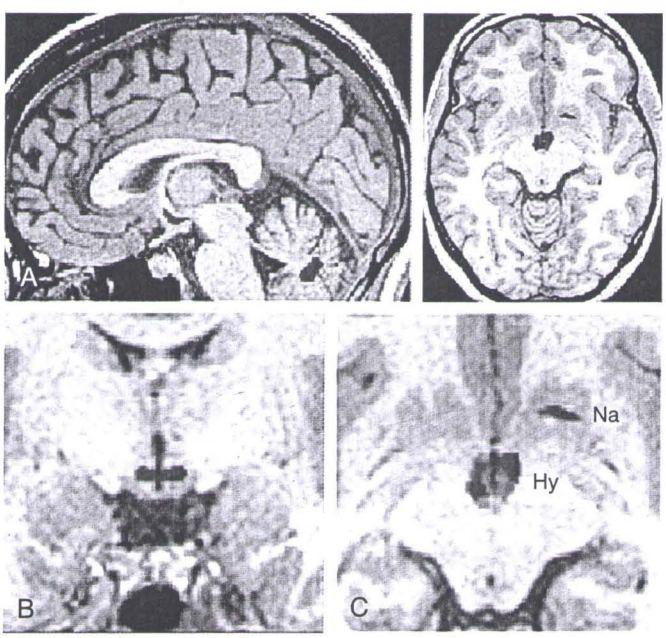

FIGURE 15–3 Statistical parametric maps demonstrating the structural difference in gray matter between narcolepsy patients and healthy control subjects. Differences are shown superimposed in red on a normalized image of a healthy control subject. The *left panel* in *A* is the left side of the brain. A significant decrease in gray matter concentration was found in the hypothalamus (Hy) (*A-C*) and in the area of the right nucleus accumbens (Na) (*A* and *C*) *(Reproduced with permission from Draganski B, Geisler P, Hajak G, et al: Hypothalamic gray matter changes in narcoleptic patients. Nat Med 2002;8:1186. Copyright 2002, Nature Publishing Group.)* (See page 207)

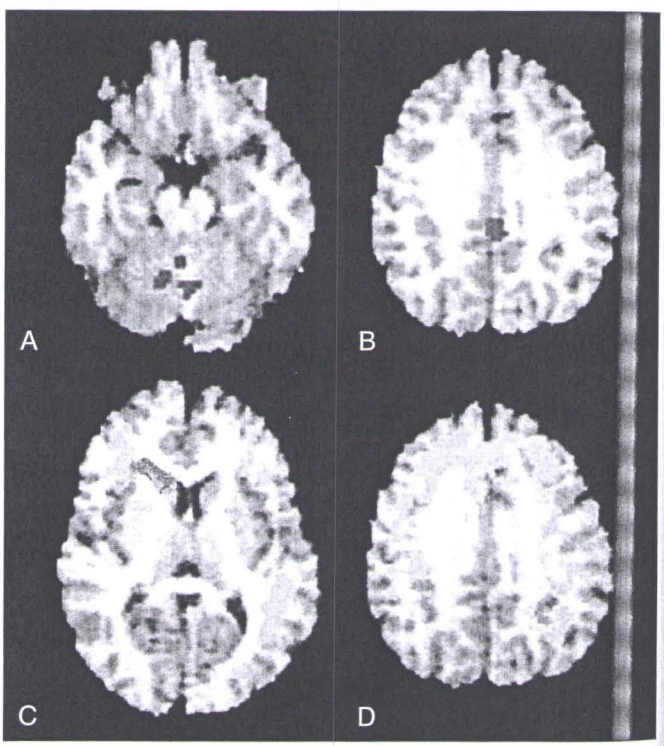

FIGURE 15–4 SPECT findings during sleepwalking after integration into the appropriate anatomic magnetic resonance image. The highest increases of regional CBF (>25%) during sleepwalking compared with quiet stage 3 to 4 NREM sleep are found in the anterior cerebellum (i.e., vermis) **(A),** and in the posterior cingulate cortex **(B).** However, as compared to data from normal volunteers during wakefulness, large areas of frontal and parietal association cortices remain deactivated during sleepwalking, as shown in the corresponding parametric maps. Note the inclusion of the dorsolateral prefrontal cortex **(C),** mesial frontal cortex **(D),** and left angular gyrus **(C)** within these areas. *(Reproduced with permission from Bassetti C, Vella S, Donati F. et al. SPECT during sleepwalking. Lancet 2000;356:484. Copyright 2000, The Lancet.)* (See page 211)

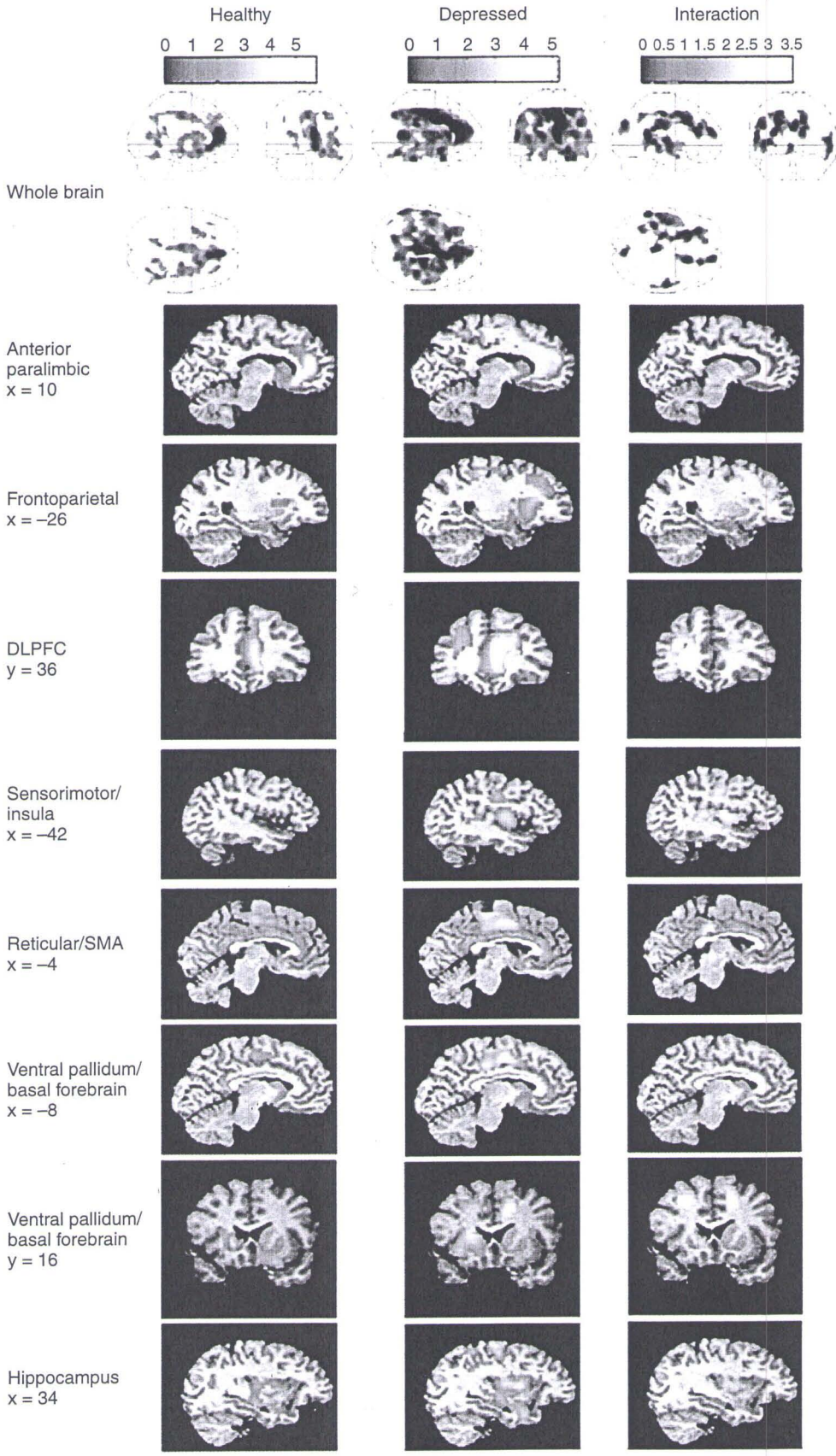

FIGURE 15–5 rCMRglu from waking to REM sleep in depression. Waking-to–REM sleep activation in healthy subjects (*column 1*) and depressed subjects (*column 2*), and interactions showing regions where the depressed subjects' waking-to–REM sleep activations are greater than those of healthy subjects (*column 3*). (DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area; x and y, Talairach *x* and *y* coordinates.) *(Reproduced with permission from Nofzinger EA, Buysse DJ, Germain A, et al: Increased activation of anterior paralimbic and executive cortex from waking to rapid eye movement sleep in depression. Arch Gen Psychiatry 2004;61:695. Copyright © 2004, American Medical Association. All rights reserved.)* (See page 215)

treatment, sleep latency was reduced by at least 43% and there was a global 24% increase in CBF, with significant increases in the basal ganglia. Smith and collaborators proposed that such increase in brain activity might reflect the normalization of sleep homeostatic processes. These encouraging initial results will certainly inspire further investigations on the effects of psychotherapy on brain functioning in insomnia.

Narcolepsy

Narcolepsy is a disorder characterized by excessive sleepiness that is typically associated with several manifestations of so-called dissociated or isolated REM sleep features, such as muscle atonia (i.e., cataplexy), sleep paralysis, and hallucinations.[106,114] Human narcolepsy has recently been found to be associated with reduction in or loss of the hypothalamic peptide hypocretin (also called orexin) implicated in arousal systems.[115–119]

Anatomic Neuroimaging Studies of Narcolepsy

The pontine tegmentum controls transitions between sleep states and was therefore first proposed as a possible main site of anatomic or functional impairments in narcolepsy. While Plazzi and coworkers had reported pontine tegmentum abnormalities in three narcoleptic patients,[120] two other structural magnetic resonance imaging (MRI) studies[121,122] found no pontine abnormalities (except in 2 of 12 patients who had long-standing hypertension[122]). The MRI abnormalities found in Plazzi et al.'s study could reflect nonspecific age-related pontine vascular changes rather than a narcolepsy-related phenomenon.[120]

More recently, studies tried to find evidence for hypothalamic abnormalities using voxel-based morphometry (VBM). VBM is a neuroimaging analysis technique that allows the investigation of focal differences in tissue composition (gray and white matter) based on high-resolution scans. To date, VBM studies have reported equivocal results in narcoleptic patients. An early study found no structural change in brains of patients with hypocretin-deficient narcolepsy.[123] Two subsequent studies did find cortical gray matter reduction predominantly in frontal brain regions,[124] as well as in inferior temporal regions.[125] Interestingly, relative global gray matter loss was independent of disease duration or medication history, and there were no significant subcortical gray matter alterations.[125] Significant gray matter concentration decreases were found in the hypothalamus, cerebellum (vermis), superior temporal gyrus, and right nucleus accumbens in 29 narcoleptic patients relative to unaffected healthy controls (Fig. 15–3).[126] Given the major projection sites of hypocretin-1 (the hypothalamus among others) and hypocretin-2 (the nucleus accumbens among others), the decreases in gray matter could thus reflect secondary neuronal losses due to the destruction of specific hypocretin

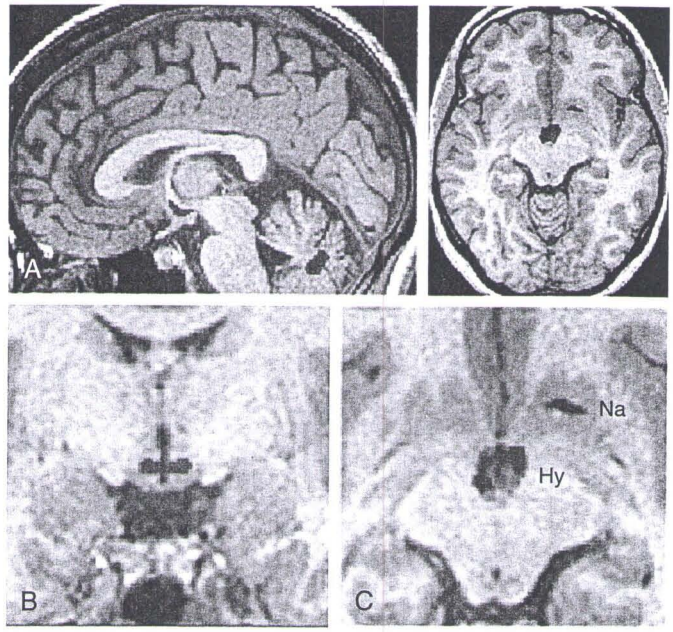

FIGURE 15–3 Statistical parametric maps demonstrating the structural difference in gray matter between narcolepsy patients and healthy control subjects. Differences are shown superimposed in red on a normalized image of a healthy control subject. The *left panel* in **A** is the left side of the brain. A significant decrease in gray matter concentration was found in the hypothalamus (Hy) (**A-C**) and in the area of the right nucleus accumbens (Na) (**A** and **C**) *(Reproduced with permission from Draganski B, Geisler P, Hajak G, et al: Hypothalamic gray matter changes in narcoleptic patients. Nat Med 2002;8:1186. Copyright 2002, Nature Publishing Group.) See Color Plate*

projections. The results of this study were recently corroborated by another VBM study.[127]

Proton magnetic resonance spectroscopy (^{1}H-MRS) was also used to assess the *N*-acetylaspartate (NAA) and creatinine plus phosphocreatinine (Cr+PCr) content in the specific brain areas of narcoleptic patients. A reduced NAA/Cr+PCr ratio indicates reduced neuronal function, which could reflect neuronal loss (i.e., fewer neurons) but could also be due to reduced activity of existing neurons. An analysis of spectral peak area ratios revealed a decrease in the NAA/Cr+PCr ratio in the hypothalamus[128] and the ventral pontine areas[129] of narcoleptic patients compared with control subjects. Several factors can explain equivocal results across both VBM and spectroscopy studies, such as inhomogeneous patient groups, history of treatment, or, for VBM, prestatistical image processing and limited sensitivity of this technique. In conclusion, VBM studies with larger samples of drug-naive patients are required to identify reliably structural abnormalities in narcolepsy.

Functional Neuroimaging Studies of Narcolepsy

Early functional observations using ^{133}Xe inhalation showed that, during wakefulness, brain stem and cerebral blood flow was lower in narcoleptic patients than in normal subjects.[130] However, after sleep onset (3 of

13 cases in REM sleep), the CBF increased in all regions, particularly in temporoparietal regions. This pattern was supposedly attributed to dreaming activity, in line with prior reports showing increased regional blood flow in temporoparietal areas during visual dreaming and hypnagogic hallucinations.[130,131]

More recently, a ^{99m}Tc-HMPAO SPECT study in six narcoleptic patients found similar HMPAO uptake in the waking state and REM sleep,[132] suggesting a similar overall cortical activity. Data analysis using regions of interest additionally indicated an activation of parietal regions during REM sleep.[132] The latter result is intriguing given the parietal deactivation usually observed by PET studies during normal REM sleep.[8] Further studies are needed to confirm these results in a larger population.

There are very few data describing the neural correlates of cataplexy in narcoleptic patients. One SPECT study was conducted on two patients during a cataplexy episode compared to REM sleep or a baseline waking period.[133] During cataplexy, perfusion increased in limbic areas (including the amygdala) and the basal ganglia, thalami, premotor cortices, sensorimotor cortices, and brain stem, whereas perfusion decreased in the prefrontal cortex and occipital lobe. Increased cingulate and amygdala activity may relate to concomitant emotional processing that is usually reported as a powerful trigger of cataplexy. However, such hyperperfusion in the pons, thalami and amygdaloid complexes was not found in a recent single case report.[134]

Based on the clinical observation that cataplexy episodes are often triggered by positive emotions (e.g., hearing or telling jokes), an event-related fMRI study was performed on narcoleptic patients and controls while they watched sequences of humorous pictures. A group comparison revealed that humorous pictures elicited reduced hypothalamic response together with enhanced amygdala response in the narcoleptic patients. These results suggest that hypothalamic hypocretin activity physiologically modulates the processing of emotional inputs within the amygdala, and that suprapontine mechanisms of cataplexy might involve a dysfunction of hypothalamic-amygdala interactions triggered by positive emotions.[135,136]

Neurotransmission in Narcolepsy

Given the role of acetylcholine as an important neurotransmitter in the generation of REM sleep (see earlier), it was hypothesized that disturbances in the cholinergic system might underlie narcolepsy. However at present, there is no existing evidence for a change in muscarinic cholinergic receptors in narcoleptic patients.[96]

Likewise, the dopamine system has been probed by PET and SPECT in narcoleptic patients because increased dopamine D_2 receptor binding was shown in the brains of deceased narcoleptic patients.[137,138] The results from these neuroimaging studies remain mostly inconsistent. One SPECT study showed elevated D_2 receptor binding in the striatal dopaminergic system, correlating with the frequency of cataplectic and sleep attacks in seven patients with narcolepsy.[139] However, other PET[140–142] or SPECT[143,144] ligand studies did not find such change in D_2 receptor binding. A potential explanation for this discrepancy might be related to the drug treatment of narcoleptic patients. Indeed, considerable increase in the uptake of ^{11}C-raclopride, a specific D_2 receptor ligand, was observed in the putamens of narcoleptic subjects older than 31 years who underwent various regimens of prolonged treatment.[145] Likewise, despite the fact that the binding of iodobenzamide (IBZM, a highly selective CNS dopamine D_2 receptor ligand), was similar in narcoleptic patients and normal controls, treatment by stimulants and/or antidepressants for 3 months significantly changed ligand uptake in four of five patients.[144] Therefore, elevated postmortem dopamine binding might be due to the long-term effect of prior treatment rather than intrinsic modifications.

Brain Response to Drug Probe in Narcolepsy

The effects of stimulant drugs on cerebral function in narcoleptic patients was assessed in two fMRI studies. The first one tested the effect of modafinil, a wakefulness-promoting drug.[97] In normal subjects, larger brain responses to a multiplexed visual and auditory stimulation paradigm were found at 10:00 AM than at 3:00 PM in visual areas, but not in auditory areas, suggesting time-of-day influences. Surprisingly, the reverse pattern of activity was observed in a group of 12 narcoleptic patients, with higher activity at 3:00 PM than 10:00 AM. Critically, modafinil administration did not modify the average level of activation either in normal subjects or in narcoleptics (n = 8), but postdrug activation level was inversely proportional to the predrug activation level. These findings are not easy to interpret but might suggest that modafinil can modulate brain activation in response to external stimuli.

Another fMRI study assessed the effects of amphetamines in two patients with narcoleptic syndrome.[146] The extent of the brain response to auditory and visual stimulation decreased after amphetamine administration in normal subjects. The reverse pattern was observed in the narcoleptic patients. Once again these findings remain difficult to interpret, and larger samples of patients should be studied. The apparent disparity of these results indicates that, despite recent breakthroughs in the pathophysiology of narcolepsy, more studies using state-of-the-art technology of acquisition and analysis of functional neuroimaging data are needed to better characterize the functional organization of the narcoleptic brain during wakefulness and sleep.

Recurrent Hypersomnia

Recurrent hypersomnia is a disorder characterized by recurrent episodes of hypersomnia that typically occur weeks or months apart.[106] One SPECT study in a

24-year-old male with recurrent hypersomnia showed decreased blood flow in the left thalamus during the hypersomnolent period, but failed to report any abnormal activation during recovery or remission periods.[147] This case report neuroimaging study provides only limited information about possible pathophysiologic mechanisms of this disorder. By contrast, other clinical and electrophysiologic studies clearly point toward a hypothalamic rather than a thalamic dysfunction.[148–150]

Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation.[106] Population-based epidemiologic studies have revealed a high prevalence (1–5% of adult men) of OSAS. They also associate OSAS with significant morbidity, such as hypertension, cardiovascular disease, stroke, and motor vehicle accidents.[151] OSAS may lead to functional and structural brain alterations. Functional alterations such as sleep fragmentation are often associated with neuropsychological deficits that can be reversible after treatment of OSAS. Structural alterations may indicate irreversible consequences on brain integrity and suggest permanent cognitive impairment, although this proposal remains a matter of debate in the literature.

The pathophysiology of OSAS is complex and not yet completely understood. Several studies suggest that OSAS across all age groups is due to a combination of both anatomic airway narrowing and abnormal upper airway neuromotor tone. Notwithstanding the known anatomic factors, such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy, that contribute to OSAS, clear anatomic contributing factors cannot always be identified.[106] This suggests that alterations in upper airway neuromuscular tone also play an important role in the etiology of OSAS.[152] The pathophysiology of OSAS also includes enhanced chemoreflex sensitivity and an exaggerated sympathetic response during hypoxemic episodes.[153]

OSAS has been associated with distinctive cognitive alterations in various domains. Both hypoxemia and fragmented sleep are proposed as the main factor leading to neurocognitive impairments during wakefulness.[154–161] Several studies emphasized the deterioration of executive functions in OSAS patients, including the inability to initiate new mental processes[162,163] and deficits in working memory,[162,163] analysis and synthesis,[162,164] contextual memory,[165] selective attention,[166] and continuous attention.[166] A recent meta-analysis showed that untreated patients with OSAS had a negligible impairment of intellectual and verbal functioning but a substantial impairment of vigilance and executive functioning.[167]

Structural changes in brain morphology were assessed using VBM in 21 patients with OSAS and in 21 control subjects.[168] Gray matter loss was apparent in patients with OSAS in multiple brain sites involved in motor regulation of the upper airway as well as in various cognitive functions, including the frontal and parietal cortices, temporal lobes, anterior cingulate, hippocampus, and cerebellum. Another VBM study conducted in seven OSAS patients and seven controls showed a significantly lower gray matter concentration restricted to the left hippocampus in the OSAS patients.[169] There was no difference in total gray matter volume between the two groups.

Another study compared both neuropathologic and neuropsychological effects of hypoxia in patients with either carbon monoxide poisoning or OSAS.[170] Brain imaging showed a hippocampal atrophy in both groups. Interestingly, a linear relationship between hippocampal volume and memory performance selectively in the OSAS group was found for a subset of tests (the delayed recall or the Rey-Osterrieth Complex Figure Design and Trail 6 of the Rey Auditory Verbal Learning Test among others). Moreover, hippocampal volume was related to performance on nonverbal information processing (Wechsler Adult Intelligence Scale–Revised Block Design) in both groups. Further investigation will be necessary to better delineate the specificity and contribution of hippocampal atrophy in OSAS.

Single-voxel ^{1}H-MRS has also been used to assess whether OSAS can induce axonal loss or dysfunction, or myelin metabolism impairment. An early study using this technique showed that the NAA/Cr ratio in cerebral white matter was significantly lower in patients with moderate to severe OSAS than in patients with mild OSAS and healthy subjects.[171] In a more recent study, the NAA/Cr and choline/creatine (Cho/Cr) ratios as well as absolute concentrations of NAA and choline were significantly lower in the frontal white matter of OSAS patients when compared to controls.[172] Even if these findings may explain some of the deficits in executive function associated with OSAS, it remains unclear whether hypoxia or sleep fragmentation is the primary cause of such dysfunction.

Consistent with the VBM results noted previously, decreases in absolute creatine-containing compounds in the left hippocampal area correlated with increased OSAS severity and worse neurocognitive performance.[173] In addition, a study by Halbower et al.[174] showed a decrease in NAA/Cho ratio in the left hippocampus and in the right frontal cortex using the same technique in a pediatric population with OSAS. Together, VBM and spectroscopy studies point to an atrophy and/or dysfunction of hippocampal regions in OSAS.

Long-term consequences of OSAS have been more rarely assessed after nasal continuous positive airway pressure (nCPAP) treatment. An early ^{99m}Tc-HMPAO SPECT study in 14 adult OSAS patients reported a marked frontal hyperperfusion in 5 patients.[175] In contrast, regional analysis showed reduced perfusion in the left parietal region. All these changes were reversed by

effective nCPAP therapy, suggesting that the main deleterious effects of OSAS on brain activity are reversible. According to the authors, there might be an apnea-associated effect of local vascular autoregulation mechanisms acting to compensate systemic blood flow alterations or blood gas changes in OSAS. In a ^{1}H-MRS study, NAA in the parieto-occipital cortex was reduced significantly more in 14 OSAS patients than in controls but, this reduction persisted after nCPAP therapy despite clinical, neuropsychological, and neurophysiologic normalization.[176] Mandibular advancement led to decreased fMRI response in the left cingulate gyrus and the bilateral prefrontal cortices in 12 healthy subjects during induced respiratory stress.[177] Simultaneously, the subjective effects of this treatment were assessed by a visual analog scale that confirmed successful reduction of respiratory stress.

Apnea episodes in OSAS patients have considerable hemodynamic consequences, which are mediated by a complex cascade of physiologic events. Repetitive episodes of apnea trigger marked fluctuations in both blood pressure and heart rate, with consequent effects on the estimates of cardiovascular variability.[5] Several important regulatory mechanisms in cardiovascular homeostasis seem to be impaired in OSAS patients. Specific chemoreceptors seem to be implicated in the pathophysiology of OSAS.[178] For instance, the ventilatory response to carbon dioxide is elevated in OSAS patients[178] due to an elevation of the partial pressure of carbon dioxide that delimits carbon dioxide ventilatory recruitment threshold. An altered autonomic balance has been suggested as one possible pathogenic factor. This autonomic dysfunction has been thought to be implicated in the subsequent development of cardiovascular diseases in patients with OSAS.

Several fMRI studies have been conducted in OSAS patients to characterize the neural correlates of integrated afferent airway signals with autonomic outflow and airway motor response.[179–182] For instance, altered response after a Valsalva maneuver involves cerebellar, limbic, and motor area gray matter loss. Enhanced sympathetic outflow after a forehead cold pressor challenge results in both diminished and exaggerated responses in the limbic area, cerebellum, frontal cortex, and thalamus.

Altogether, these findings suggest that neuropsychological deficits in OSAS might relate to various alterations in the prefrontal cortex, hippocampus, and parietal cortex. Even if abnormal brain activations are reversible under nCPAP, several studies have suggested that not all neuropsychological impairments disappear after nCPAP.[163,183,184] Although the basic pathophysiologic mechanisms are not completely understood, a dysregulation in autonomic control seems to play an important role. However, some peripheral factors may also contribute to the deficits observed in OSAS patients, including exaggerated mass index and motivational problems.[185,186]

Periodic Limb Movements

Periodic limb movement disorder (PLMD) during sleep and restless legs syndrome (RLS) are distinct but overlapping disorders. PLMD is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep.[106] RLS is a disorder characterized by disagreeable leg sensations, usually prior to sleep onset, that cause an almost irresistible urge to move the legs.[106]

The diagnosis of PLMD does require the presence of periodic limb movements in sleep (PLMS) on polysomnography as well as an associated sleep complaint. A diagnosis of RLS, however, is essentially made on clinical grounds. Moreover, PLMS are themselves nonspecific, occurring both with RLS and with other sleep disorders (e.g., narcolepsy, sleep apnea syndrome, REM sleep behavior disorder) as well as in normal individuals.[187] Thus, the diagnosis of PLMD requires the exclusion of other potential causes for the associated sleep complaint.[188]

An inhibition of descending inhibitory pathways implicating dopaminergic, adrenergic, and opiate systems is thought to be involved in PLMS pathogenesis.[189] Patients' condition worsens when dopamine antagonists are given,[190] whereas dopaminergic drugs have been shown to relieve PLMS.[191–193] Staedt et al. have tested the hypothesis of a decrease dopaminergic activity in PLMS patients. In a series of SPECT studies, they report a decreased IBZM striatal uptake, indicating a lower D_2 receptor occupancy in PLMS patients.[194–197] Treating patients with dopamine replacement therapy increased the IBZM binding and improved the sleep quality in these patients.[196]

As RLS responds to dopaminergic medications, an etiologic link between RLS and Parkinson's disease (PD) has been hypothesized. However, a study demonstrated that RLS was present in only 15.2% of PD patients. Moreover, the prevalence of RLS in PD patients was very similar to the prevalence in the general population or a clinic population, suggesting that these two diseases may not share the same pathophysiologic mechanisms.[198]

Fourteen patients with idiopathic RLS and PLMS with a good response to dopaminergic and nondopaminergic treatment were investigated while off medication by using ^{123}I-IBZM and SPECT.[199] They were compared to 10 healthy, sex- and age-matched control subjects. The patients presented sleep disturbances, severe PLMS, and severe RLS symptoms during the period of scanning and did not show any significant differences in striatal-to-frontal ^{123}I-IBZM binding to D_2 receptors compared to controls, contrary to the previous study. These findings suggest the recovery of normal D_2 receptor function in successfully treated patients with idiopathic RLS and PLMS.[199]

One study evaluated the striatal pre- and postsynaptic dopamine status in 10 drug-naive patients suffering from

both RLS and PLMS and 10 age-matched controls, by means of ^{123}I methyl-3β-(4-iodophenyl)tropane-2β-carboxylate (^{123}I-β-CIT), a ligand of dopamine transporter, and ^{123}I-IBZM SPECT, respectively.[200] There was no difference in dopamine transporter (^{123}I-β-CIT) binding between RLS-PLMS patients and controls. The study of the striatal D_2 receptor binding (^{123}I-IBZM) revealed again a significantly lower binding in patients as compared with controls. Numerous mechanisms may be responsible for the decrease of the D_2 receptor binding. Since ^{123}I-β-CIT binding is normal, a decreased number of D_2 receptors or a decreased affinity of D_2 receptors for ^{123}I-IBZM is more likely than a down-regulation of D_2 receptors due to an increased level of synaptic dopamine.[200]

Structural cerebral abnormalities have recently been reported in patients with idiopathic RLS.[201] High-resolution T1-weighted MRI of 51 patients and 51 controls analyzed using VBM revealed a bilateral gray matter increase in the pulvinar in patients with idiopathic RLS. These authors suggest that changes in thalamic structures are either involved in the pathogenesis of RLS or may reflect a consequence of chronic increase in afferent input of behaviorally relevant information. Finally, an fMRI study also attempted to localize some cerebral generators of leg discomfort and periodic limb movements in RLS.[202] During leg discomfort, the study showed a bilateral activation of the cerebellum and contralateral activation of the thalamus in patients. During a second condition combining periodic limb movements and sensory leg discomfort, patients also showed activity in the cerebellum and thalamus with additional activation in the red nuclei and brain stem close to the reticular formation. Interestingly, when subjects were asked to voluntarily imitate PLMS, there was no activation in the brain stem, but rather additional activation in the globus pallidus and motor cortex. These results suggest an involuntary mechanism of induction and a subcortical origin for RLS.

Taken together, these studies support the hypothesis that a central dopamine dysfunction is involved in the pathophysiology of RLS and PLMS, although more recent studies specifically implicate the cerebral metabolism of iron.[203] However, iron and the dopaminergic system are linked since iron is an important cofactor for tyrosine hydroxylase, the step-limiting enzyme in dopamine synthesis, and also plays a major role in the functioning of postsynaptic D_2 receptors.[5] Consistent with a link between the dopaminergic system and iron, Allen et al.[204] found decreased regional iron concentrations in the substantia nigra and putamens of five patients with RLS, both in proportion to RLS severity. In addition, Earley et al.[205] found diminished iron concentration across 10 brain regions in early-onset RLS patients but not in late-onset RLS patients when compared to controls.

Sleepwalking

Sleepwalking is an arousal parasomnia consisting of a series of complex behaviors that result in large movements during sleep.[206] It is perceived as a dissociation state whereby most of the brain sleeps except motor-related areas. One 16-year-old male subject was studied during sleepwalking using ^{99m}Tc-labeled ethyl cysteinate dimer SPECT.[207] Compared to awake normal volunteers (n = 24), a decrease in rCBF in the frontoparietal associative cortices and an increase in rCBF in the posterior cingulate cortex were found, suggesting that this state dissociation arose from combined activation of thalamocingulate pathways and persisting deactivation of other thalamocortical arousal systems (Fig. 15–4).

REM Sleep Behavior Disorder

This condition, initially described by Schenck et al.,[208] is characterized by brisk movements of the body associated with dream mentation during REM sleep that usually disturbs sleep continuity. During the nocturnal spells, patients behave as if they were acting out their dream.[106]

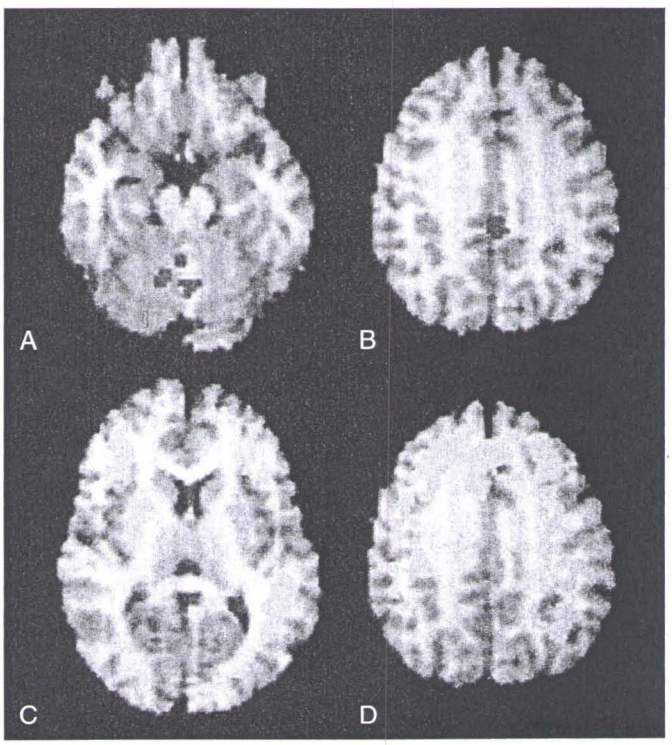

FIGURE 15–4 SPECT findings during sleepwalking after integration into the appropriate anatomic magnetic resonance image. The highest increases of regional CBF (>25%) during sleepwalking compared with quiet stage 3 to 4 NREM sleep are found in the anterior cerebellum (i.e., vermis) **(A),** and in the posterior cingulate cortex **(B).** However, as compared to data from normal volunteers during wakefulness, large areas of frontal and parietal association cortices remain deactivated during sleepwalking, as shown in the corresponding parametric maps. Note the inclusion of the dorsolateral prefrontal cortex **(C),** mesial frontal cortex **(D),** and left angular gyrus **(C)** within these areas. *(Reproduced with permission from Bassetti C, Vella S, Donati F, et al. SPECT during sleepwalking. Lancet 2000;356:484. Copyright 2000, The Lancet.) See Color Plate*

This disease may be idiopathic (up to 60%) or associated with other neurologic disorders. A sizeable proportion of patients with REM sleep behavior disorder (RBD) will develop extrapyramidal disorders,[209–211] Lewy body dementia,[212] and multiple system atrophy (MSA).[213,214] More recently, a strong association between RBD and α-synucleinopathies has been observed, with the parasomnia often preceding the clinical onset of the neurodegenerative disease.[212]

Interestingly, an early experimental model of RBD in the cat has shown that lesions in the mesopontine tegmentum can lead to the disappearance of muscle atonia during REM sleep together with dream-enactment behavior.[215]

A study combining MRI and ^{123}I-IMP SPECT in 20 patients with RBD and 7 healthy controls during REM sleep reported significantly decreased blood flow in the upper portion of both sides of the frontal lobe and pons in patients with RBD, in comparison with normal elderly subjects.[216] Another SPECT study in eight RBD patients during waking rest showed decreased activity in the frontal and temporoparietal cortices but found increased activity in the pons, putamen, and right hippocampus.[217] In addition, an increased Cho/Cr ratio in the brain stem suggesting local neural abnormalities was revealed by ^{1}H-MRS in a 69-year-old man with idiopathic RBD as compared with healthy adults.[218] In contrast, one ^{1}H-MRS study, conducted in 15 patients with idiopathic RBD and 15 matched control subjects, failed to reveal any difference in metabolic peaks of NAA/Cr, Cho/Cr, and myoinositol/creatine ratios in the pontine tegmentum and the midbrain.[219] Whether idiopathic RBD involves mesopontine neuronal loss or ^{1}H-MRS–detectable metabolic disturbances therefore remains unsettled.

Using SPECT and IPT (a ligand of striatal presynaptic dopamine transporter), IPT binding in RBD patients (n = 5) during wakefulness was found to be lower than in normal controls but higher than in PD patients (n = 14).[220,221] These results suggest that the number of presynaptic dopamine transporters is decreased in both PD and RBD patients. Other studies probed the density of striatal dopaminergic terminals using PET and ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ, a monoamine vesicular transporter inhibitor used as an in vivo marker for dopaminergic nerve terminals). Significant reductions in striatal ^{11}C-DTBZ binding characterized 6 elderly subjects with chronic idiopathic RBD, as compared to 19 age-matched controls, particularly in the posterior putamen.[222] Likewise ^{11}C-DTBZ binding in the striatum was decreased in 13 patients with MSA.[214] Striatal ^{11}C-DTBZ uptake was inversely correlated with the severity of symptoms in this MSA group. Moreover ^{123}I-iodobenzovesamiol (^{123}I-IBVM) binding was reduced in the thalamus in this MSA population. ^{123}I-IBVM is a radiotracer that selectively binds to the intraneuronal storage vesicles of cholinergic nerve endings, and is used as a highly specific marker for cerebral cholinergic neurons.

It remains to be shown whether theses alterations play a causal role in the pathophysiology of RBD or reflect functional consequences and adaptations to the pathologic conditions. Although there is evidence that some PD patients do show excessive nocturnal movements,[197,223] it is interesting that only a small percentage of PD patients develop full-blown RBD. This suggests that modifications of other systems of neurotransmission are probably necessary for full-blown RBD to occur.

Sleep Functional Imaging in Mental Disorders

Psychoses

Psychoses are psychiatric disorders characterized by the occurrence of delusions, hallucinations, incoherence, catatonic behavior, or inappropriate affects that cause impaired social or work functioning. Insomnia or excessive sleepiness is a common feature of psychoses.[106]

Schizophrenia is a major, devastating psychosis that affects approximately 1% of the population irrespective of culture, social status, or gender. The pathophysiology of schizophrenia is complex and remains poorly understood. There are different, nonexclusive, pathophysiologic theories of schizophrenia, including neurotransmitter dysfunction, developmental abnormalities, and genetic susceptibilities.[224] The most robust theory has focused on dysfunction of the neurotransmitters dopamine and glutamate.[224]

Schizophrenia, as a syndrome, is composed of a variety of relatively specific core symptoms.[225] These can be divided into positive and negative symptoms. The former include hallucinations, delusions, and disorganization, and the latter comprise anergia, flattening of affect, and poverty of thought content. Additional characteristics are disorganization (including bizarre thoughts and behavior) and cognitive function disturbances.

The negative symptoms of schizophrenia have been related to the decrease of cerebral activity in frontal areas.[226] It was suggested that each characteristic symptom reflects a specific pattern of abnormal cerebral activity in associative frontal, parietal, or temporal regions, and in related subcortical structures. During the performance of executive tasks, schizophrenic subjects exhibit impaired frontal activation, and during memory tasks they show impaired temporal lobe activation. However, abnormalities seem to be mainly subtended by a disturbed connectivity between cerebral areas rather than by specific regional dysfunctions.[227] Sleep problems are common in schizophrenia. Polysomnographic abnormalities seem to occur consistently in schizophrenic patients, including sleep-onset and maintenance insomnia, reduced amounts of SWS, reduced REM sleep latency, and defective REM rebound following REM deprivation.[228,229]

However, these findings are not specific to schizophrenia. Furthermore, only a subgroup of schizophrenic patients presents these abnormalities. Reduced SWS is thought to reflect a neurodevelopmental disorder,[228] and was linked to impairments in visuospatial memory in schizophrenics.[230]

It remains controversial whether reduced SWS in schizophrenia relates either directly or indirectly to an underlying brain dysmorphology. In schizophrenic patients, a close association between SWS and ventricular volume was found in one study[231] but not in another study.[232]

Finally, similarities between dreams and schizophrenia delusions and hallucinations might suggest that cerebral activity in schizophrenia is comparable to cerebral activity during REM sleep.[233] However, this hypothesis is not supported by a PET study that investigated the relationship between REM sleep and schizophrenia.[234] Glucose consumption during REM sleep in 12 controls was found to differ largely from cerebral activity in 49 awake schizophrenic patients and 30 awake controls.

Mood Disorders

Mood disorders constitute a psychiatric condition that is characterized by either one or more episodes of depression, or partial or full manic or hypomanic episodes. Typical sleep disturbances in mood disorders are insomnia and, more rarely, excessive sleepiness.[106] The association between insomnia and depression is not clearly understood.

Depression is the most common primary diagnosis in patients suffering from insomnia.[235] In addition, depressed patients frequently report increased daytime fatigue and tend to compensate with daytime napping. However, sleep disturbances appear to vary even across depression subtypes. For instance, patients with bipolar disorder report insomnia while depressed, but also hypersomnia, with extended nocturnal sleep periods, difficulty awakening, and excessive daytime sleepiness.[235] In addition, depression is associated not only with insomnia but also with other sleep disorders such as OSAS and hypersomnolence.[236] Here, we only focus on the links between depression and insomnia.

Neuroimaging studies in depressed patients during wakefulness suggest that dysfunctions within the prefrontal cortical and striatal systems that normally modulate limbic and brain stem structures play a role in the pathogenesis of depressive symptoms.[237] Abnormalities within orbital and medial prefrontal cortex areas persist following symptom remission.[237] These findings involve interconnected neural circuits in which dysfunction of neurotransmission may result in depressive symptoms.[237,238]

We first present the hyperarousal hypothesis, which links depression to insomnia. Next, we review studies conducted during NREM and REM sleep in depressed patients. Finally, we discuss results pertaining to the use of sleep deprivation as a treatment in depression.

Hyperarousal Hypothesis. In depressed patients, modifications of sleep architecture are characterized by reduced SWS, early onset of the first episode of REM sleep, and increased phasic REM sleep.[239] In addition to daytime tiredness, patients often report persistent and disturbing mental activity when getting asleep. In addition to cognitive and emotional hyperarousal, physiologic hyperarousal has been described. According to Clark and Watson, this physiologic hyperarousal reflects an anxiety component in anxiety-depression disorder.[240–242] Interestingly, hyperarousal has been described in idiopathic insomnia (see earlier). Moreover, risk of depression as a comorbid state appears to be particularly strong in insomnia patients.[243]

Intriguingly, sleep deprivation has rapid beneficial effects on about 60% of depressed patients.[244] Responders to sleep deprivation are usually patients with high behavioral activation and low levels of tiredness.[245,246] These findings suggest increased arousal in depressed patients,[240,245,247] a hypothesis that found some support in functional neuroimaging data. Beta activity was proposed as an EEG marker of arousal during sleep. In an ^{18}FDG PET study,[248] beta power was negatively correlated with subjective sleep quality in both normal and depressed subjects, although depressed patients exhibited increased beta activity during the night versus normal controls. Interestingly beta power was correlated with glucose metabolism levels in the ventromedial prefrontal cortex, a region among the most deactivated during consolidated SWS (see earlier).[248]

These clinical, electrophysiologic, and neuroimaging studies indicate hyperarousal in depressed patients. Nevertheless, the exact pathophysiologic mechanisms linking hyperarousal and insomnia to depression are still unclear.

NREM Sleep Neuroimaging in Depression. An early study indicated that whole-brain absolute CMRglu during NREM sleep is higher in depressed patients than in normal subjects.[249] The greatest increases were observed in the posterior cingulate, amygdala, hippocampus, and occipital and temporal cortices. Significant reductions of relative CMRglu were found in the prefrontal and anterior cingulate cortices, caudate nucleus, and medial thalamus.

In a more recent study, depressed patients showed less decrease than controls in relative rCMRglu from presleep wakefulness to NREM sleep in the left and right laterodorsal frontal gyri, right medial prefrontal cortex, right superior and middle temporal gyri, insula, right posterior cingulate cortex, lingual gyrus, striate cortex, cerebellar vermis, and left thalamus.[250] This finding suggests that transition from wakefulness to NREM sleep in depressed patients might be characterized by relatively persistent "elevated" activity in the frontoparietal regions and

thalamus. Intuitively, it is as if the low frontal metabolism during wakefulness could not be further decreased during NREM sleep, as is the case for normal subjects. These findings suggest that abnormal thalamocortical network function may underlie sleep anomalies and nonrestorative sleep complaints in depressed patients.[250]

REM Sleep Neuroimaging in Depression. All the available data to date have been obtained by using the ^{18}FDG PET method. Due to radiation exposure limitation, a restricted number of scan can be acquired in a single patient, which limits the statistical power of the results. Therefore, great care must be taken in the interpretation of the results, which should be viewed as preliminary.

During REM sleep as compared to wakefulness, anterior paralimbic areas (anterior cingulate cortex, right insula, right parahippocampal gyrus) were found to be less active in depressed patients than in normal subjects.[251] Conversely, another study by the same group showed that, while both healthy and depressed patients activate anterior paralimbic structures from waking to REM sleep, the spatial extent of this activation was greater in depressed patients (Fig. 15–5).[252] Moreover, depressed patients showed greater activation in the bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, as well as in the midbrain reticular formation[252] and in the tectal area, inferior temporal cortex, amygdala, and subicular complex[251] from waking to REM sleep.

The severity of the depression has been found to correlate with the density of rapid eye movement (number of such movements per minute of REM sleep).[253,254] In depressed patients compared to healthy controls, average REM count (an automated analog of REM density) was positively correlated with rCMRglu bilaterally in the striate cortex, the posterior parietal cortices, and the medial and ventrolateral prefrontal cortices and negatively correlated with rCMRglu in areas corresponding bilaterally to the lateral occipital cortex, cuneus, temporal cortices, and parahippocampal gyri.[255] For the authors, these results suggested that average REM count may be a marker of hypofrontality during REM sleep in depressed patients.

Bupropion, an antidepressant drug, increased activity in the anterior cingulate, medial prefrontal cortex, and right anterior insula from waking to REM sleep in depressed patients, due to a reduction in waking relative metabolism in these structures following treatment in the absence of a significant effect on REM sleep–related metabolism.[98]

Sleep Deprivation in Depression. Sleep deprivation has profound effects on brain metabolism in both normal and depressed subjects. As stated previously, sleep deprivation relieves acute depressive symptoms in 60% of patients. In depressed patients responding favorably to sleep deprivation, baseline brain activity during wakefulness was reported to be higher in responders than in nonresponders in the anterior cingulate cortex[256,257] and/or the nearby mesial frontal cortex.[257–260] This activity was significantly decreased after sleep deprivation. A similar profile of brain activation was observed in elderly depressed patients, including normalization after total sleep deprivation associated with antidepressant treatment.[261] Moreover, the normalization of anterior cingulate metabolism persisted even after recovery sleep.[261] It was also shown that sleep deprivation responders exhibit a significant decrease in relative basal ganglia D_2 receptor occupancy after sleep deprivation, as compared to nonresponders.[262] These results suggest that the antidepressant benefits of sleep deprivation are correlated with enhanced endogenous dopamine release in responders. These results corroborate previous hypotheses about the role of dopaminergic response in the therapeutic action of sleep deprivation, and indirectly support a dopamine hypothesis of depression.[262]

In combination with data obtained during REM sleep in depressed patients, sleep deprivation data suggest a tight link between mood alteration and activity in limbic and paralimbic structures. The data suggest that anterior cingulate hyperactivity in depressed patients during wakefulness may hinder further increases during REM sleep. Hence, sleep deprivation may alleviate depression symptoms by decreasing abnormally elevated activity in the anterior cingulate cortex during wakefulness. However, available data remain limited, and further studies are needed to understand the causes and consequences of these mesial frontal metabolic disturbances.

Sleep Functional Imaging in Neurologic Disorders

Fatal Familial Insomnia

Fatal familial insomnia (FFI), a hereditary or sporadic disease caused by prion-protein gene mutation, is characterized by insomnia, autonomic hyperactivity and motor abnormalities.[263,264] This disease is invariably lethal.[263] The disrupted sleep profile is characterized by a loss of sleep spindles and SWS, and enacted dreams during REM sleep.[264] In four awake patients investigated using ^{18}FDG PET, a prominent hypometabolism was observed in the anterior part of the thalamus.[265] Two patients exhibited symptoms restricted to insomnia and dysautonomia. Thalamic hypometabolism was found isolated in one subject, accompanied by frontal, anterior cingulate, and temporal polar hypometabolism in the other. In the two patients who had a more complex clinical presentation, hypometabolism was more widespread and involved many cortical areas, the basal ganglia, and the cerebellum. This widespread pattern was already present at an early stage of the disease and was found to be significantly aggravated as the disease progressed in one patient examined twice several months apart. However, it is not known

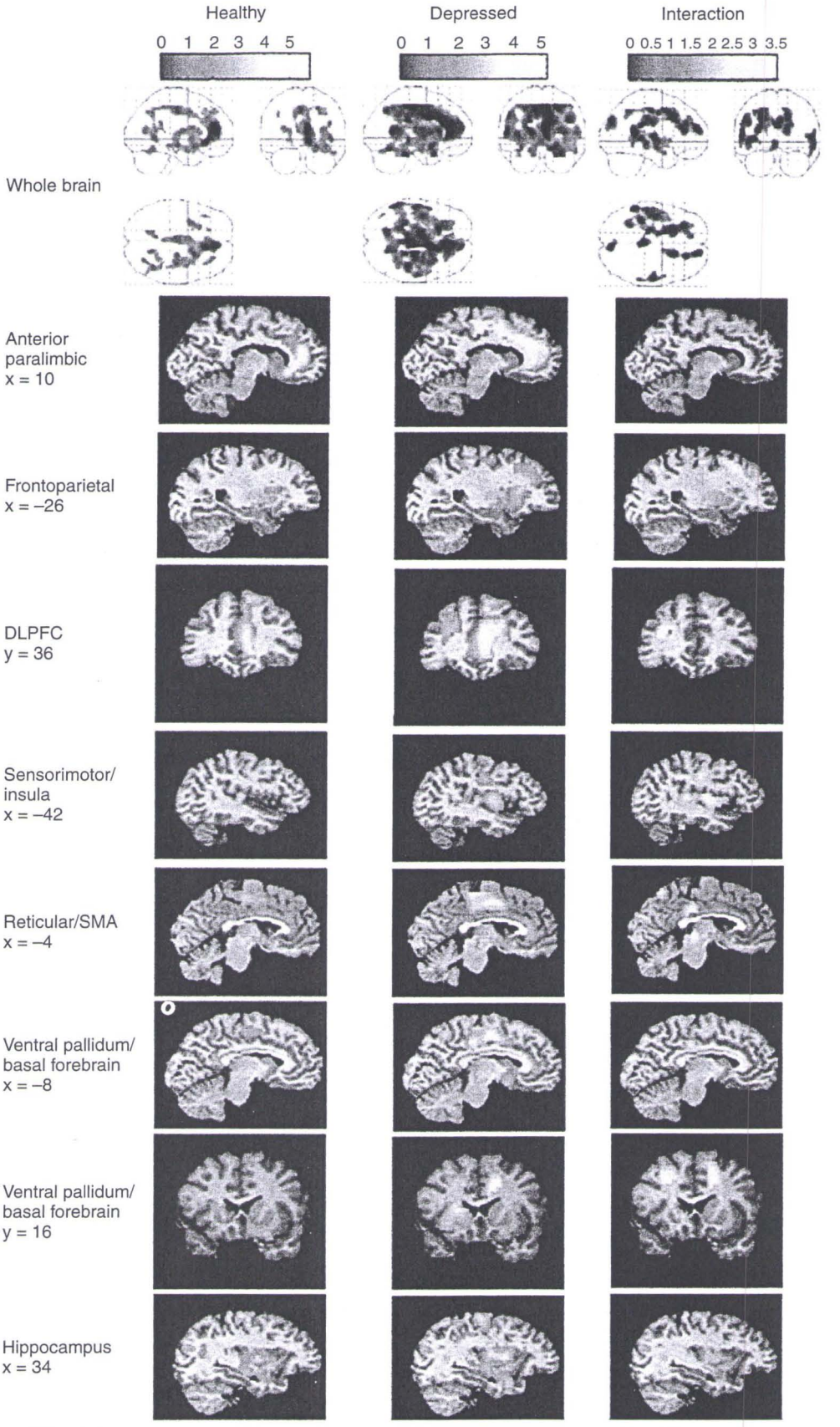

FIGURE 15–5 rCMRglu from waking to REM sleep in depression. Waking-to–REM sleep activation in healthy subjects (*column 1*) and depressed subjects (*column 2*), and interactions showing regions where the depressed subjects' waking-to–REM sleep activations are greater than those of healthy subjects (*column 3*). (DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area; x and y, Talairach *x* and *y* coordinates.) *(Reproduced with permission from Nofzinger EA, Buysse DJ, Germain A, et al: Increased activation of anterior paralimbic and executive cortex from waking to rapid eye movement sleep in depression. Arch Gen Psychiatry 2004;61:695. Copyright © 2004, American Medical Association. All rights reserved.) See Color Plate*

whether this widespread hypometabolism is indicative of the more advanced stages of the disease or whether it indicates two forms of this disorder, one thalamic and the other disseminated.

Another study used ^{18}FDG PET to examine regional cerebral glucose utilization in seven patients with FFI.[266] Severely reduced glucose utilization in the thalamus and a mild hypometabolism in the cingulate cortex were found in all FFI patients. In six of these subjects, brain hypometabolism also affected the basal and lateral frontal cortex, caudate nucleus, and middle and inferior temporal cortices. Further comparison between homozygous (n = 4) or heterozygous (n = 3) patients at codon 129 showed that the hypometabolism was more widespread in the heterozygous group, which had a significantly longer symptom duration at the time of ^{18}FDG PET study. Comparison between neuropathologic and ^{18}FDG PET findings in six patients showed that areas with neuronal loss were also hypometabolic. However, cerebral hypometabolism was more widespread than expected by histopathologic changes, and significantly correlated with the presence of a protease-resistant prion protein. Neuroimaging results indicated that hypometabolism of the thalamus and cingulate cortex is a common feature of FFI, while the involvement of other brain regions depends on the duration of symptoms and some unknown factors specific to each patient.[266] Even in a case of atypical FFI, thalamic hypometabolism was confirmed as an early marker while cortical changes varied with clinical presentation and stage.[267]

More recently, serotonin function was examined in two FFI patients with ^{123}I-β-CIT SPECT and compared to age-expected control values.[268] This study showed a dramatic reduction in serotonin transporter availability in a diencephalic region for both FFI patients. Although this finding suggests an involvement of serotonin neurotransmission, it is not clear whether it is causal in the FFI pathogenesis.[268]

The Landau-Kleffner Syndrome and Related Disorders

The Landau-Kleffner syndrome (LKS) and the syndrome of continuous spike-and-wave discharges during SWS (CSWS) were originally described separately and are still considered as distinct pathophysiologic entities. LKS is characterized by acquired aphasia and paroxysmal sleep-activated EEG predominating over the temporal or parieto-occipital regions. Paroxysmal events are spike-and-wave discharges that are activated by SWS. Secondary symptoms include psychomotor or behavioral disturbances and epilepsy, with a favorable outcome for seizure control.[269] CSWS is characterized by continuous spike-and wave discharges during SWS, usually combined with global intellectual deterioration and epileptic seizures.[270] Both syndromes share many features in common, including early onset during childhood, deterioration of cognitive function (previously acquired normally), seizure type, EEG pattern, and pharmacologic reactivity. They also have in common the regression of neuropsychological symptoms, EEG abnormalities, and seizures before the end of adolescence. Early reports found no structural brain lesions detectable by computed tomography or MRI.[269–272] However, more recent MRI volumetric analyses performed in four children with typical LKS revealed volume reduction in bilateral superior temporal areas, specifically the planum temporale and superior temporal gyrus, where receptive language is localized.[273,274]

Initial functional imaging studies using PET[269,275–278] and SPECT[277,279–285] described metabolic abnormalities in LKS that predominantly involved the temporal lobes. Focal or regional areas of decreased and increased metabolism were reported. A normal distribution of CBF was reported in one isolated case.[286] These early results were difficult to interpret in terms of pathogenesis.

Later on, cerebral glucose metabolism was investigated using ^{18}FDG PET in a larger population of asleep and awake patients.[287,288] Again regional increases and decreases in cerebral glucose metabolism were observed. The metabolic patterns were found to be variable from one patient to another, and grossly related to the neuropsychological deterioration. Moreover, metabolic patterns in individual patients were reported to change over time. Interestingly, another PET study showed that residual impairment in verbal short-term memory after recovery was probably linked in two of three LKS patients with significantly less activation than controls in their left and right posterior superior temporal gyrus during immediate serial recall of lists of 4 words, compared to single-word repetition. One patient having near-normal short-term memory performance showed increased activity in the posterior part of the right superior temporal gyrus. According to the authors, these results suggested that impaired verbal short-tem memory at late outcome of LKS might be related to a persistent decrease of activity in those posterior superior temporal gyri that were involved in the epileptic focus during the active phase.[289]

Voxel-based analyses of cerebral glucose metabolism were performed in a group of 18 children with CSWS using statistical parametric mapping. Each patient was compared with a control group, and the influence of age, epileptic activity, and corticosteroid treatment on metabolic abnormalities was assessed. Cerebral metabolic patterns were heterogeneous across patients with CSWS. Age and intensity of awake interictal spiking did not significantly differ in patients showing focal hypermetabolism compared with the others. Treatment with corticosteroids corrected focal hypermetabolism. Altered parietofrontal connectivity observed in patients with hypermetabolism was interpreted as a phenomenon of remote inhibition of the frontal lobes induced by the highly epileptogenic and hypermetabolic posterior cortex.[290]

Studies in LKS patients indicated four basic metabolic characteristics. First, LKS patients have a higher rate of metabolism in the cortical mantle than in the thalamic nuclei. This metabolic pattern is characteristic of an immature brain. Second, they show focal or regional metabolic abnormalities of the cortex, suggesting a focal origin of the spike-and-wave discharges. Third, they have metabolic disturbances predominantly involving associative cortices, suggesting deterioration of cognitive function only. Fourth, glucose metabolism in thalamic nuclei remains symmetric despite significant cortical asymmetries, suggesting that corticothalamic neurons either do not participate in the generation of spike-and-wave discharges or are being inhibited by pathologic mechanisms.

These studies also suggest that CSWS is produced by an alteration in the maturation of one or more associative cortices, potentially leading to disturbed neuronal wiring. An imbalance of inhibitory and excitatory drives would lead to deterioration in associated higher cerebral functions and would create conditions contributing to the production of neuronal discharges. Discharges expressed during waking would be activated during SWS because of the physiologic reinforced synchronization of neuronal firing characteristic of that type of sleep.[291]

CONCLUSIONS

Functional neuroimaging provides unprecedented possibilities to explore brain function during normal and pathologic sleep. Nevertheless, neuroimaging in sleep is still in its infancy, at present mostly restricted to research purposes. A major research effort should be developed in order to better characterize pathophysiologic mechanisms of sleep disorders, teasing apart functional causes from consequences. Functional neuroimaging could also be helpful to assess the functional and structural consequences of long-term sleep disruption. These efforts should benefit from advanced multimodal neuroimaging and improved experimental designs.

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