Chapter 6

Functional neuroimaging in sleep, sleep deprivation, and sleep disorders

MARTIN DESSEILLES *, THANH DANG VU, AND PIERRE MAQUET
Cyclotron Research Centre, University of Liège, Belgium

INTRODUCTION

The optimal management of patients with sleep disorders would require a comprehensive understanding of the underlying specific pathological mechanisms, but also an exact appreciation of the consequences of ensuing sleep disruption. The latter objective is hampered by our incomplete knowledge of normal sleep. During the last 50 years, considerable progress has been made in the understanding of the neural mechanisms by which sleep is induced, maintained, and regulated (McCarley et al., 1983; Buzsaki, 1998; Kryger et al., 2000; Saper et al., 2001; Steriade and Timofeev, 2003). Yet, at present, our understanding remains fragmentary and we are still striving for a comprehensive description of sleep mechanisms. Likewise, the functions of sleep are not yet undisputedly specified, although several hypotheses have been proposed (Maquet et al., 2003). Consequently, the effect of sleep on cerebral and bodily functions (Stickgold and Walker, 2007), as well as the consequences of sleep deprivation or fragmentation (Chee and Chuah, 2008), are not yet fully understood at the different levels of description.

Neuroimaging studies conducted in sleep disorders have suffered from this fragmentary knowledge of normal sleep. For instance, they often have not been able to tease apart the pathological mechanisms of a given disorder from the consequences of the ensuing sleep disruption. Nevertheless, impressive advances have been made in some sleep disorders. In this section, our aim is to describe the present state of the art and hopefully exemplify the limitations of the available neuroimaging literature. The review begins with a short account of neuroimaging studies conducted during normal sleep, because they nicely introduce the subsequent pathological sections.

NEUROIMAGING IN NORMAL HUMANS

Introduction

Studies using positron emission tomography (PET), single photon emission computed tomography (SPECT) or functional magnetic resonance imaging (fMRI) reviewed in this section have shown that global and regional patterns of brain activity during sleep are outstandingly different from wakefulness. These studies also demonstrated the persistence of brain responses to external stimuli during sleep as well as plastic changes in brain activity related to previous waking experience.

Nonrapid eye movement (NREM) sleep

NREM sleep, when compared to wakefulness or REM sleep (Maquet et al., 1997; Maquet, 2000), is characterized by a global decrease in cerebral blood flow (CBF), and by a regional deactivation in the dorsal pons, mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain and anterior hypothalamus, prefrontal cortex, anterior cingulate cortex and precuneus. This distribution of brain activity could be at least partially explained by NREM sleep generation mechanisms in mammals (Maquet et al., 1990). Taking into account that PET measurements average cerebral activity over 90 seconds to 45 minutes, decreases in CBF and metabolism during NREM are thought to reflect a change in firing pattern, characterized by synchronized bursting activity followed by long hyperpolarization periods, more than a decrease in the average neuronal firing rate (Maquet, 2000). Accordingly, as compared to wakefulness, the average

---

*Correspondence to: Martin Desseilles, MD, PhD, Cyclotron Research Centre, University of Liège, Bâtiment B30, 8, allée du 6 Août – B-4000 Liège (Belgium). Tel: +32 4 366 23 16, Fax: +32 4 366 29 46, E-mail: m.desseilles@ulg.ac.be

cerebral metabolism and blood flow levels begin to decrease in light (stage 1 and 2) NREM sleep (Madsen et al., 1991b; Maquet et al., 1992; Kjaer et al., 2002), and are the lowest during deep (stage 3 and 4) NREM sleep, also named slow-wave sleep (SWS) (Maquet et al., 1990; Madsen et al., 1991a).

NREM sleep rhythms (spindles, delta, and slow oscillations) are generated by a cascade of events occurring in thalamoneocortical networks, initially induced by a decreased activation from the brainstem tegmentum (Steriade and Amzica, 1998). Accordingly, in humans, brainstem blood flow is decreased during light NREM sleep (Kajimura et al., 1999) as well as during SWS (Braun et al., 1997; Maquet et al., 1997; Kajimura et al., 1999; Nofzinger et al., 2002). However, 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 (Kajimura et al., 1999). In SWS, both

pontine and mesencephalic tegmenta are deactivated (Maquet et al., 1997).

The thalamus occupies a central position in the generation of NREM sleep rhythms like spindles and delta waves, due to the intrinsic oscillating properties of its neurons and to the intrathalamic and thalamo-cortico-thalamic connectivity. As expected, in humans, regional CBF decreases have been found in the thalamus during both light and deep NREM sleep (Braun et al., 1997; Maquet et al., 1997; Kajimura et al., 1999), and also in proportion to the power density of the electroencephalogram (EEG) signal in the spindle frequency range (Hofle et al., 1997). However, in a recent study, regional CBF was not correlated with delta activity in the thalamus (Dang-Vu et al., 2005), suggesting the potential active participation of the cortex in the generation of the delta rhythm recorded on the scalp (Figure 6.1).

The role of the cortex in the generation of NREM sleep oscillations (e.g., slow cortical rhythm) begins to
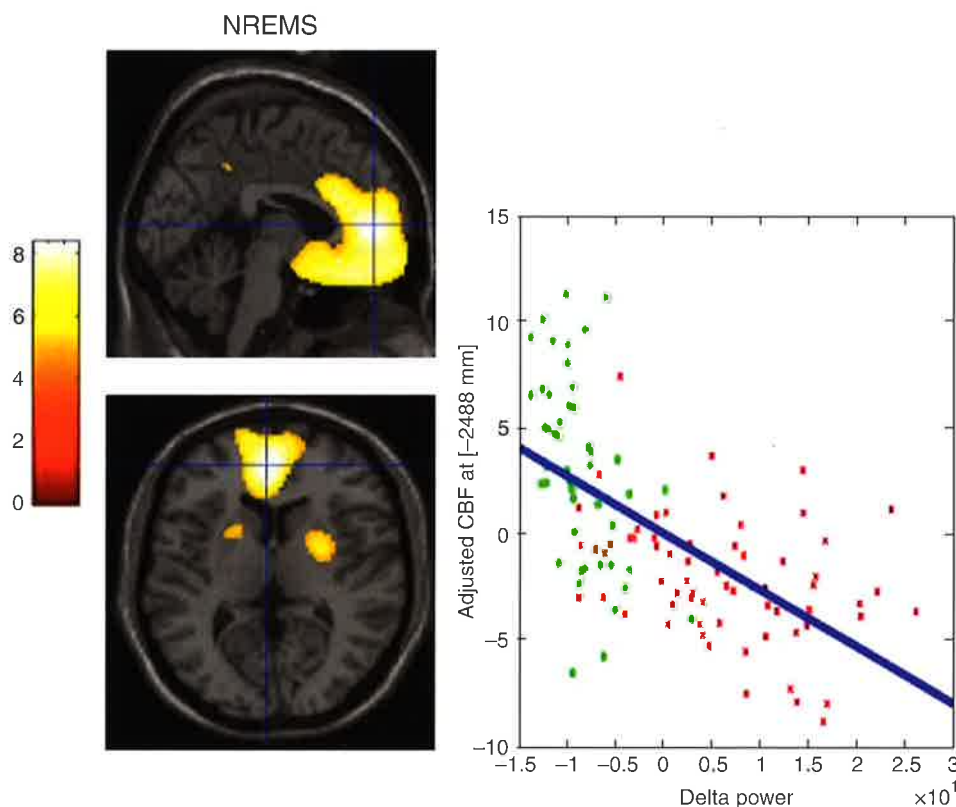
Fig. 6.1. Regional cerebral blood flow (rCBF) decrease as a function of delta power during nonrapid eye movement (NREM) sleep.

Left panel: rCBF decreases as a function of delta power during NREM sleep. Image sections are centered on the ventromedial prefrontal cortex. The color scale indicates the range of Z values for the relevant voxels.

Right panel: Plot of the adjusted rCBF responses (arbitrary units) in the ventromedial prefrontal cortex in relation to the adjusted delta power values (μV^2) during NREM sleep corresponding to left panel pictures: rCBF activity decreases when delta power increases. Each circle/cross represents one scan: green circles are stage 2 scans, red crosses are stage 3–4 scans. The blue line is the linear regression. (Reprinted from Dang-Vu et al., 2005; copyright (2005). Reprinted with permission from Elsevier.)

be understood at the microscopic system level (Steriade et al., 1993). Their neural correlates at the macroscopic system levels are less well characterized. EEG 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 (Finelli et al., 2001). 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), parietal, and to a lesser extent in the temporal and insular, lobes (Braun et al., 1997; Maquet et al., 1997; Andersson et al., 1998; Kajimura et al., 1999). In contrast the primary cortices were the least deactivated cortical areas (Braun et al., 1997). A linear (inverse) relationship between delta waves and rCBF is also found in ventromedial prefrontal regions during NREM sleep (Dang-Vu et al., 2005). 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 (Borbely, 2001), these cortices might be more profoundly influenced by SWS rhythms than primary cortices (Maquet, 2000).

The predominance of slow oscillation-related rCBF decreases in ventromedial prefrontal regions may be functionally important since these cortical regions, known to deteriorate after a short sleep deprivation (Horne, 1988, 1993; Pilcher and Huffcutt, 1996; Harrison and Horne, 1998, 1999), are involved in mood regulation and in various cognitive functions (such as planning or probability matching) (Harrison and Horne, 1999) that help in adapting individual behavior. Studies of the deleterious effects of sleep deprivation on human cognition also pointed to an exquisite sensitivity of these association cortices to sleep deprivation (see below).

Recent studies have used simultaneous EEG/fMRI recordings during NREM sleep to characterize the neural correlates of NREM sleep oscillations in healthy humans. In contrast to PET studies that described the patterns of brain activity during the different sleep stages or correlated with values of EEG spectral power, the better temporal resolution of fMRI allows assessment of the brain activity changes directly related to brief events such as spindles and delta waves. Spindles have been associated with increases of brain activity in the thalamus, anterior cingulate cortex, insula, and superior temporal gyrus (Schabus et al., 2007). Delta waves have been associated with increases of brain activity in the inferior frontal gyrus, brainstem, cerebellum,

precuneus, posterior cingulate cortex, and parahippocampal gyrus (Dang-Vu et al., 2008). Beside identifying the brain structures involved in the generation, propagation, or modulation of NREM sleep oscillations, these studies emphasize that NREM sleep is not a state of brain quiescence characterized by persistent decrease in brain activity, but a state during which brain activity is temporally organized in specific oscillations.
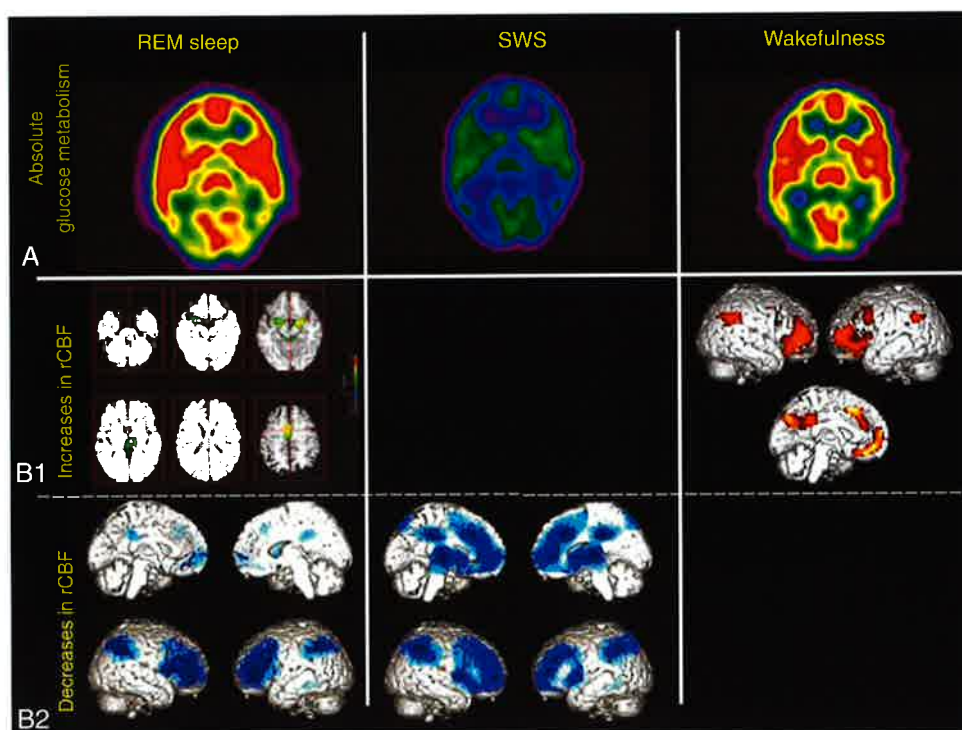
REM sleep

In contrast to NREM sleep, REM sleep is characterized by a sustained neuronal activity (Steriade and McCarley, 1990; Jones, 1991) and, correspondingly, by high cerebral requirements (Maquet et al., 1990) and blood flow (Madsen et al., 1991a; Lenzi et al., 1999) (Figure 6.2). In this active but sleeping brain, some areas are particularly active, even more than during wakefulness, while others have lower than average regional activity.

During REM sleep, significant rCBF increases have been found in the pontine tegmentum, thalamic nuclei, limbic and paralimbic areas (amygdaloid complexes (Maquet et al., 1996; Nofzinger et al., 1997), hippocampal formation (Braun et al., 1997; Nofzinger et al., 1997), and anterior cingulate cortex (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997)). Posterior cortices in temporo-occipital areas were also found to be activated (Braun et al., 1997; Wehrle et al., 2005), although less consistently. In contrast, the inferior and middle dorsolateral prefrontal gyri and the inferior parietal cortex were the least active brain regions (Maquet et al., 1996, 2005; Braun et al., 1997).

Regional brain activity in mesopontine, occipital, and thalamic regions during human REM sleep (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997; Wehrle et al., 2005) 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 activate the thalamic nuclei which in turn activate the cortex (Steriade and McCarley, 1990).

The activation of limbic and paralimbic structures, including amygdaloid complexes, hippocampal formation, and anterior cingulate cortex, is constantly reported (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997). Animal data show that the amygdala plays a role in REM sleep modulation. For example, ponto-geniculo-occipital (PGO) waves, a major component of REM sleep phasic endogenous activity, were increased in cats by electrical stimulation of the central nucleus of amygdaloid complexes (Calvo et al., 1987), while carbachol (cholinergic agonist) injections in the same nucleus enhanced both REM sleep and PGO activity (Calvo et al., 1996).

Fig. 6.2. Cerebral glucose metabolism (CMRGlu) and regional cerebral blood flow (rCBF) during rapid eye movement (REM) sleep (first column), deep non-REM (NREM) sleep or slow-wave sleep (SWS) (second column), and wakefulness (third column).

Row A: CMRGlu quantified in the same individual at 1-week interval, using ^{18}F-fluorodeoxyglucose and positron emission tomography (PET). The three images are displayed at the same brain level using the same color scale. The average CMRGlu during deep NREM sleep (versus wakefulness) is significantly decreased. During REM sleep the CMRGlu 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, the thalami, the amygdaloid complexes, and the anterior cingulate cortex. Other data (not shown) have shown a large activity in the occipital cortices, the insula, and the hippocampus (Braun et al., 1997).

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 brainstem and thalami are also particularly deactivated.

Likewise, the rebound of REM sleep induced by microinjections of gamma aminobutyric acid (GABA) agonist into the periaqueductal gray matter elicited a significant increase in c-fos labeling in the amygdala (Sastre et al., 2000).

The activated temporo-occipital areas during REM sleep (Braun et al., 1997) include inferior temporal cortex and fusiform gyrus, which are extrastriate cortices belonging to the ventral visual stream. Functional connectivity of these areas is also modified during REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory during wakefulness, is reversed during REM sleep (Braun et al., 1997, 1998). Likewise, the functional relationship between the amygdala and the temporal and occipital cortices is different during REM sleep than during wakefulness

or NREM sleep (Maquet and Phillips, 1998). This pattern suggests that not only the functional neuroanatomy but also the functional interactions between neuronal populations are different during REM sleep than during wakefulness.

Pontine waves or 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 enthorinal cortex, the hippocampus, and the amygdala, as well as brainstem structures participating in the generation of REM sleep (Datta et al., 1998). In cats, although most easily recorded in the pons (Jouvet, 1967), the lateral geniculate bodies (Mikiten et al., 1961), and the occipital cortex (Mouret et al., 1963), PGO waves are observed in many parts of the brain,

including limbic areas (amygdala, hippocampus, cingulate gyrus) (Hobson, 1964). Using PET, regional CBF in the lateral geniculate bodies and the occipital cortex was shown to be more tightly coupled to spontaneous eye movements during REM sleep than during wakefulness (Peigneux et al., 2001). These data are in keeping with other pieces of evidence suggesting the existence of pontine waves in humans, and have been more recently corroborated by an fMRI study (Wehrle et al., 2005). In epileptic patients, direct intracerebral recordings in the striate cortex showed monophasic or diphasic potentials during REM sleep, isolated or in bursts (Salzarulo et al., 1975). In normal subjects, surface EEG revealed transient occipital and/or parietal potentials time-locked to the REMs (McCarley et al., 1983). Source dipoles of magnetoencephalography signal were localized in the brainstem, thalamus, hippocampus and occipital cortex during REM sleep (Inoue et al., 1999; Ioannides et al., 2004).

The brain remains reactive to external stimulation during sleep

Available functional neuroimaging data globally suggest that the processing of external stimuli persists during NREM sleep. 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 (Portas et al., 2000). Moreover, the left amygdala and the left prefontal cortex were found to be more activated by subjects' own name than by pure tones, and more so during sleep than during wakefulness, suggesting the persistence during sleep of specific responses for meaningful or emotionally loaded stimuli.

In contrast, other groups observed that response to auditory stimulation was decreased during sleep as compared to wakefulness (Czisch et al., 2002). Intriguingly, the brain activation pattern of visual stimulation during SWS in adults showed a decrease in activity in the rostromedial occipital cortex (Born et al., 2002). This decrease was more rostral and dorsal compared to the relative regional CBF 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 replication (Czisch et al., 2004).

NEUROIMAGING IN SLEEP DISORDERS

Introduction

In this section, we will mainly focus on primary sleep disorders. We will include several types of dyssomnia related to intrinsic sleep disorders (e.g., idiopathic

insomnia, narcolepsy, and obstructive sleep apnea), abnormal motor behavior during sleep (e.g., periodic limb movement disorder and REM sleep behavior disorder (RBD)). Sleep may also be secondarily disrupted in a number of conditions ranging from environmental causes (e.g., jet lag, shift work, noisy environment) to medical diseases (e.g., endocrine disorders, chronic pain, brain lesions) and psychiatric disorders (e.g., anxiety, depression, schizophrenia). From the latter conditions, we will only consider the sleep disorders secondary to depression.

Single case reports of brain functional imaging like in recurrent hypersomnia (Nose et al., 2002) and in sleepwalking (Bassetti et al., 2000) as well as rare disorders such as fatal familial insomnia, Landau–Kleffner syndrome and the syndrome of continuous spike-and-wave discharges during slow wave sleep are not reviewed.

Idiopathic insomnia

Idiopathic insomnia is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality of the neurological control of the sleep–wake system (AASM, 2001). This disorder is thought to reflect an imbalance between the arousal system and the various sleep-promoting systems (AASM, 2001). In particular, hyperactivity within the arousal system is presently believed to be the final common pathway of the disorder (AASM, 2001). For instance, 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 (Stepanski et al., 1988; Bonnet and Arand, 1995, 1997). In addition, poor sleep leads to altered mood and motivation, decreased attention and vigilance, low levels of energy and concentration, and increased daytime fatigue (AASM, 2001).

Quantitative EEG recordings suggest an overall cortical hyperarousal in insomnia (Perlis et al., 2001). However, it should be noticed that hyperarousal in primary insomnia was characterized by an increase in beta/gamma activity at sleep onset, followed by a decline leading to a brief period of hypoarousal (Perlis et al., 2001). Accordingly, some neuroimaging studies show a cortical hyperarousal pattern in insomnia while others report a decrease in cortical functions. In the latter, decreased metabolism might originate from the time window coincidence of the cortical hypoarousal period with neuroimaging acquisition, and therefore does not discard the hyperarousal hypothesis of primary insomnia (Smith et al., 2002).

Only a small number of studies tried to characterize the functional neuroanatomy of idiopathic insomnia

disorder (referred to as primary insomnia in these reports). Using technetium-99m-hexamethylene-propyleneamine Oxime (^{99}mTC-HMPAO), a gamma-emitting radionuclide imaging agent, regional CBF was estimated in 5 insomniacs and 4 normal sleepers during NREM sleep. Patients with insomnia revealed major rCBF decreases in the basal ganglia, frontal medial, occipital, and parietal cortices. These results suggest that idiopathic insomnia is associated with an abnormal pattern of regional brain function during NREM sleep that particularly involves basal ganglia (Smith et al., 2002).
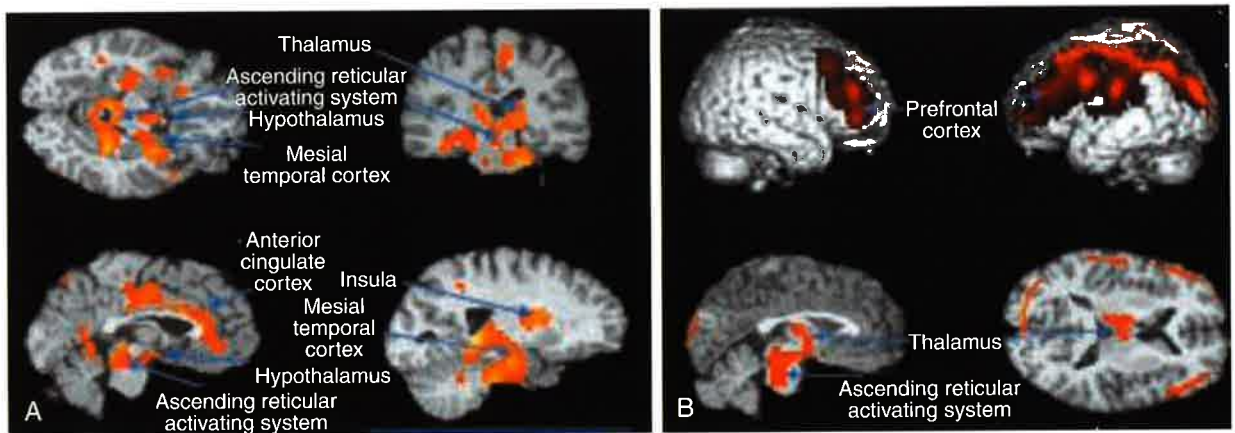
More recently, regional cerebral glucose metabolism (CMRglu) was measured using ^{18}F-fluorodeoxyglucose (^{18}FDG) PET in 7 patients with idiopathic insomnia and 20 healthy age- and gender-matched subjects during waking and NREM sleep (Nofzinger et al., 2004a). Insomniac patients showed increased global CMRglu during sleep as compared to healthy subjects, suggesting an overall cortical hyperarousal in insomnia. In addition insomniac patients had a smaller decline, related to healthy subjects, in CMRglu from waking to sleep states in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices. During wakefulness, reduced metabolism, as compared to healthy subjects, was detected in the prefrontal cortex bilaterally, in the left superior temporal, parietal, and occipital cortices and in the thalamus, hypothalamus, and brainstem reticular formation. Taken together, these findings confirm that regional brain activity does not normally progress from waking to sleep states in patients with

insomnia. Moreover, it was proposed that daytime fatigue resulting from inefficient sleep may be reflected by decreased activity in the prefrontal cortex (Nofzinger et al., 2004a) (Figure 6.3).

Interestingly, 4 of the insomnia patients from the Smith's study were rescanned after cognitive behavioral therapy (Smith et al., 2005). Sleep latency was reduced by at least 43% and there was a global 24% increase in CBF, with significant increases in the basal ganglia after this psychotherapeutic treatment. Such an increase in brain activity has been proposed to reflect the normalization of sleep homeostatic processes. These promising results will certainly inspire further investigations on the effects of psychotherapy on brain functioning in insomnia.

Depression

The most common primary diagnosis in patients presenting with a complaint of insomnia is depression (Benca, 2000). Depression is a subclass of mood disorders, which are psychiatric disorders characterized by either one or more episodes of depression, or partial or full manic or hypomanic episodes. Depressive disorders include major depressive disorder, diagnosed in people who have experienced at least one major depressive episode. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV: American Psychiatric Association, 1994) provides diagnostic criteria for major depression. At least five symptoms must be present for the same 2-week period, nearly every day, and at least one symptom must be either depressed

Fig. 6.3. Regional cerebral glucose metabolism (CMRGlu) in patients with insomnia assessed during both waking and nonrapid eye movement sleep states by using ^{18}F-fluorodeoxyglucose positron emission tomography.

Panel A: Brain structures that did not show decreased glucose metabolic rate from wakefulness to sleep states in patients with insomnia.

Panel B: Brain structures where relative glucose metabolism during wakefulness was higher in healthy subjects than in patients with insomnia. (Reproduced from Nofzinger et al. (2004a), with permission from the American Journal of Psychiatry, Copyright 2004. American Psychiatric Association.)

mood or loss of interest or pleasure. Other symptoms of major depressive episodes include insomnia or hypersomnia, significant weight loss or weight gain, psychomotor activity or retardation, fatigue, feelings of worthlessness or excessive or inappropriate guilt, poor concentration, recurrent thoughts of death, and recurrent suicidal ideation. The disease is classified as dysthymic when the full criteria for major depression are not met and when individuals are chronically depressed for at least 2 years. The association between typical features of depression, insomnia, and, more rarely, excessive sleepiness (AASM, 2001) remains not clearly understood.

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 (Thase, 1998).

In the following sections, we will present studies conducted in depressed patients during wakefulness, after sleep deprivation, during NREM, and during REM sleep.

WAKEFULNESS NEUROIMAGING IN DEPRESSION

Neuroimaging studies in depressed patients during wakefulness indicate that dysfunction of the prefrontal cortical and striatal systems, which normally modulate limbic and brainstem structures, play an important role in the pathogenesis of depressive symptoms (Mayberg, 1997; Drevets, 2001). Abnormalities within orbital and medial prefrontal cortex areas persist following symptom remission (Drevets, 2000). These findings involve interconnected neural circuits in which dysfunction of neurotransmission may result in the depressive symptoms (Drevets, 2000, 2001).

The Hamilton Depression Rating Scale (HDRS) is widely used to measure the severity of depression in mood disorders. Voxelwise correlation maps have shown that total HDRS score correlates with metabolism as measured by ^{18}F-FDG PET during wakefulness in a large set of cerebral areas, including limbic structures, thalamus, and basal ganglia. Moreover, sleep disturbance, a distinct symptom cluster included in the HDRS, correlated positively with glucose metabolism in limbic structures and basal ganglia (Milak et al., 2005).

SLEEP DEPRIVATION IN DEPRESSION

Intriguingly, sleep deprivation has rapid beneficial effects in about 60% of depressed patients (Wirz-Justice and Van den Hoofdakker, 1999). Responders to sleep deprivation are usually patients with high behavioral activation and low levels of tiredness (Szuba et al., 1991; Bouhuys et al., 1995). These findings

suggest an increased arousal in depressed patients (Clark and Watson, 1991; Joiner et al., 1999), a hypothesis that finds support in functional neuroimaging data. Beta activity is proposed as an EEG marker of arousal during sleep. In an [18]FDG PET study (Nofzinger et al., 2000) 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 compared to normal controls. Interestingly, beta power was correlated with glucose metabolism levels in the ventromedial prefrontal cortex, a region amongst the most deactivated during consolidated SWS (see above) (Nofzinger et al., 2000).

These clinical, electrophysiological, and neuroimaging studies provide some evidence in keeping with the hypothesis of increased hyperarousal in depressed patients. Nevertheless, pathophysiological mechanisms linking hyperarousal with depression as well as insomnia with depression remain to be established.

The physiological mechanisms underpinning the beneficial effects of sleep deprivation are complex and not completely understood yet. It has been hypothesized that REM sleep pressure is enhanced in depressed patients. In depressed patients responding favorably to sleep deprivation, as compared to nonresponders, baseline brain activity during wakefulness was reported to be higher in the anterior cingulate cortex (Wu et al., 1992; Clark et al., 2001) and/or the nearby mesial frontal cortex (Ebert et al., 1991, 1994b; Wu et al., 1999; Clark et al., 2001), then to decrease significantly after sleep deprivation as compared to wakefulness. A similar pattern of brain activity was observed in elderly depressed patients, including normalization after total sleep deprivation associated with antidepressant treatment (Smith et al., 1999). In addition, the normalization of anterior cingulate metabolism persisted even after recovery sleep (Smith et al., 1999). Interestingly, it was also shown that sleep deprivation responders, as compared to nonresponders, exhibit a significant decrease in relative basal ganglia D2 receptor occupancy after sleep deprivation (Ebert et al., 1994a). These results suggest that the antidepressant benefits of sleep deprivation are correlated with enhanced endogenous dopamine release in responders, as compared to nonresponders. These results corroborate previous hypotheses of dopaminergic participation in the therapeutic action of sleep deprivation, and indirectly support a dopamine hypothesis of depression (Ebert et al., 1994a).

Recently, a preliminary work studied the effect of concomitant sleep deprivation and antidepressant medication in 6 depressed patients (Wu et al., 2008). They were administered the serotonergic antidepressant sertraline for a week and then underwent FDG

PET before and after total sleep deprivation. Glucose metabolism decreased in the inferior frontal gyrus and inferior frontal/orbital frontal cortex and increased in the dorsolateral prefrontal cortex, in correlation with reduced score of HDRS.

NREM SLEEP NEUROIMAGING IN DEPRESSION

It was shown that whole-brain absolute CMRglu during NREM sleep is higher in depressed patients than in normal subjects (Ho et al., 1996). The greatest increases were observed in the posterior cingulate, the amygdala, the hippocampus, and the occipital and temporal cortex. Significant reductions of relative CMRglu were found in the prefrontal and anterior cingulate cortices, caudate nucleus, and medial thalamus.

More recently, depressed patients showed smaller decreases than controls in relative regional CMRglu 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 (Germain et al., 2004b). These results suggest that transition from wakefulness to NREM sleep in depressed patients is characterized by persistent "elevated" activity in 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 underpin sleep abnormalities and nonrestorative sleep complaints in depressed patients (Germain et al., 2004b).

REM SLEEP NEUROIMAGING IN DEPRESSION

Anterior paralimbic areas (anterior cingulate cortex, right insula, right parahippocampal gyrus) were shown to be less active in depressed patients than in normal subjects, during REM sleep, as compared to wakefulness (Nofzinger et al., 1999). The spatial extent of paralimbic activation from waking to REM sleep was shown to be greater in the depressed patients as compared to healthy controls (Nofzinger et al., 2004b). Moreover, from waking to REM sleep, depressed patients showed greater activation in bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, as well as in the midbrain reticular formation (Nofzinger et al., 2004b) and in the tectal area, inferior temporal cortex, amygdala, and subicular complex (Nofzinger et al., 1999).

The density of REM (number of REMs per minute of REM sleep) has been correlated with the severity of the depression (Thase et al., 1997; Buysse et al., 1999).

Average REM count (an automated analog of REM density) was positively correlated with regional CMRglu bilaterally in the striate cortex, the posterior parietal cortices, and in the medial and ventrolateral prefrontal cortices in depressed patients compared to healthy controls. Moreover, it was negatively correlated with regional CMRglu in areas corresponding bilaterally to the lateral occipital cortex, cuneus, temporal cortices, and parahippocampal gyri (Germain et al., 2004a). For the authors, these results suggest that average REM count may be a marker of hypofrontality during REM sleep in depressed patients.

Bupropion (an antidepressant drug) increases CMRglu in anterior cingulate, medial prefrontal cortex, and right anterior insula from waking to REM sleep. After analysis, this effect was linked to a reduction in waking relative metabolism in these structures following treatment in the absence of a significant effect on REM sleep relative metabolism (Nofzinger et al., 2001).

SUMMARY

Taken together, these data suggest a close link between mood alteration and activity in limbic and paralimbic structures. Especially, it suggests that hyperactivity in the anterior cingulate cortex of depressed patients during wakefulness may hinder further increases in REM sleep. From this perspective, sleep deprivation would alleviate depression symptoms in decreasing abnormally elevated activity in the anterior cingulate cortex during wakefulness. However, available data remain limited and further studies using more detailed designs are needed to understand the causes and consequences of these mesial frontal metabolic disturbances.

Overall, relationships between sleep, insomnia, and depression open a neurobiological window to the understanding of the pathophysiological mechanisms of depression which should be extensively exploited in the future.

Narcolepsy

Narcolepsy is a disorder which is characterized by excessive sleepiness that is typically associated with cataplexy, sleep paralysis, and hypnagogic hallucinations (AASM, 2001).

To the best of our knowledge, in narcoleptic patients, the voxelwise functional neuroanatomy of waking state, REM sleep, or SWS is not yet fully described. Nor are the neural correlates characterized of other characteristic symptoms such as cataplexy, hypnopompic/hypnagogic hallucinations, or sleep paralysis.

Early observations using ^{133}Xe inhalation showed that, during wakefulness, brainstem and cerebellar

blood flow was lower in narcoleptic patients than in normal subjects (Meyer et al., 1980). In contrast, after sleep onset (3 out of 13 in REM sleep), the CBF increased in all areas, and particularly in temporoparietal regions. This pattern was supposedly attributed to dreaming activity, in line with prior reports showing that regional blood flow was increased in temporoparietal areas during visual dreaming and hypnagogic hallucinations (Meyer et al., 1980, 1987).

In another study, 6 narcoleptic patients underwent [99]mTC-HMPAO SPECT and showed similar HMPAO uptake in waking state and REM sleep (Asenbaum et al., 1995), suggesting a similar overall cortical activity. An activation of parietal regions during REM sleep was shown with data analysis by regions of interest (Asenbaum et al., 1995). The latter result is intriguing given the parietal deactivation usually observed by PET studies during normal REM sleep (Maquet, 2000). Overall, further studies are needed to confirm these results on a broader population.

Data describing the neural correlates of cataplexy in narcoleptic patients are very scarce. One SPECT study was conducted on 2 patients during a cataplexy episode compared to REM sleep or baseline waking period (Hong et al., 2006). During cataplexy, perfusion increased in limbic areas (including amygdala) and basal ganglia, thalami, premotor cortices, sensorimotor cortices, and brainstem, whereas perfusion decreased in 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 (Chabas et al., 2007).

A very recent event-related fMRI study was performed on narcoleptic patients and controls while they watched sequences of humorous pictures. This study is based on the clinical observation that cataplexy episodes are often triggered by positive emotions (e.g., hearing or telling jokes). 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 (Schwartz et al., 2008). Another fMRI study confirmed an increase of activity in the emotional network in narcoleptic patients as compared to controls while viewing humorous cartoons (Reiss et al., 2008). Increased activity was also observed in the right inferior frontal gyri,

an area involved in inhibition (Aron et al., 2004). In addition a reduction in hypothalamic activity was shown in 1 subject experiencing a cataplectic attack. For authors, these findings suggest an overdrive of the emotional circuitry and possible compensatory suppression by cortical inhibitory regions in cataplexy (Reiss et al., 2008).

Given the role of acetylcholine as an important neurotransmitter in the generation of REM sleep (see above), cholinergic dysfunction was hypothesized to underlie narcolepsy. However, at present, the available PET data did not show any change in muscarinic cholinergic receptors in narcoleptic patients (Sudo et al., 1998).

Similarly, the dopamine system has been probed by PET in narcoleptic patients because increased dopamine D2 binding was shown in the brain of deceased narcoleptic patients (Aldrich et al., 1992; Kish et al., 1992). Results remain controversial. One SPECT study has shown that D2 receptor binding in the striatal dopaminergic system was elevated and correlates with the frequency of cataplectic and sleep attacks in 7 patients with narcolepsy (Eisensehr et al., 2003a). However, this finding was not confirmed by other PET (Rinne et al., 1995, 1996; MacFarlane et al., 1997) or SPECT (Hublin et al., 1994; Staedt et al., 1996) studies. This discrepancy might be related to the drug treatment of narcoleptic patients. Indeed, considerable increase in the uptake of ^{11}C-raclopride, a specific D2 receptor ligand, was observed in the putamen of narcoleptic subjects older than 31 years who had undergone prolonged treatment (Khan et al., 1994). Likewise, despite the fact that the binding of iodobenzamide (IBZM, a highly selective central nervous system dopamine D2 receptor ligand) was similar in narcoleptic patients and normal controls, treatment by stimulants and/or antidepressants for 3 months significantly changed the ligand uptake in 4 out of 5 patients (Staedt et al., 1996). Collectively, these neuroimaging results suggest that the reported postmortem increase in dopamine binding might be due to the long-term effect of prior treatment rather than intrinsic modifications.

Two fMRI studies assessed the effects of stimulant drugs on cerebral function in narcoleptic patients. The first one tested the effect of modafinil, a wakefulness-promoting drug (Ellis et al., 1999). In normal subjects, larger brain responses to a multiplexed visual and auditory stimulation paradigm were found at 10.00 hours than at 15.00 hours 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 15.00 hours than at 10.00 hours. Additionally, modafinil administration did not modify the average level of activation in either normal subjects or narcoleptics

($n = 8$), but postdrug activation level was inversely proportional to the predrug activation level. These findings are not easy to interpret but at least suggest that modafinil can modulate brain activation to external stimuli. The second study used fMRI and assessed the effects of amphetamines in a small sample of patients with narcoleptic syndrome ($n = 2$) (Howard et al., 1996). As compared to 3 normal control subjects, the extent of the brain response to auditory and visual stimulation decreased after amphetamine administration in normal subjects. The reverse pattern was observed in narcoleptic patients. Once again, data are very scarce, these findings remain difficult to interpret, and larger samples should be studied before any generalization can be made.

Interestingly, using SPECT in 21 healthy volunteers, modafinil has been shown to increase wakefulness and regional CBF in the arousal-related systems and in brain areas related to emotion and executive function (including thalami, dorsal pons, frontopolar, orbitofrontal, superior frontal and middle frontal gyri, insular gyri, cingulate gyrus, inferior temporal gyri, and parahippocampal gyrus) (Joo et al., 2008). Despite these results, it is not clear if activity elicited by wake-promoting drug is underpinned by the same network in narcoleptic patients and healthy controls.

Finally, narcolepsy has been linked to a loss of hypothalamic neurons producing orexin (hypocretin), a neuropeptide implicated in arousal systems (Lin et al., 1999). Hypocretin neurons are localized in the lateral hypothalamus and have widespread excitatory projections throughout the brainstem, basal forebrain, and spinal cord. Hypocretin neurons receive in turn inputs from excitatory (glutaminergic) and inhibitory (noradrenergic, serotonergic, and GABAergic) neurons (Baumann and Bassetti, 2005). Hypocretin neurons are hypothesized to be implicated in maintaining wakefulness (Sakurai, 2005) and regulating motor functions (locomotion, muscle tone), energy expenditure (Sakurai, 2005), and sympathetic activity (Baumann and Bassetti, 2005). In humans, postmortem autopsy studies showed a loss of hypocretin mRNA and absence of hypocretin peptides in the hypothalami of narcoleptic patients (Peyron et al., 2000; Thannickal et al., 2003). Low cerebrospinal fluid (CSF) hypocretin-1 levels are usual findings in narcolepsy with definite cataplexy (Mignot et al., 2002). In contrast, in most patients with narcolepsy without cataplexy and in other primary sleep–wake disorders (such as insomnia or restless-legs syndrome (RLS)), CSF hypocretin-1 levels are normal (Baumann and Bassetti, 2005). Moreover, the CSF hypocretin-1 levels have been found to be low in several neurological disorders, irrespective of sleep habits (see, for instance, in advanced Parkinson's disease, Drouot et al. (2003)).

These elements suggest that hypocretin deficiency may represent in specific clinical contexts a marker of hypothalamic dysfunction rather than an immediate cause of sleep–wake disturbance (Baumann and Bassetti, 2005).

Differences in brain morphology that are not identifiable in routine structural MRI can be investigated using the technique of voxel-based morphometry (VBM) that compares the brain structure of patients and controls assessed by high-quality MRI (Ashburner and Friston, 2000, 2001). At present, VBM studies have reported equivocal results in narcoleptic patients. A first study did not show any structural change in brains of patients with hypocretin-deficient narcolepsy (Overeem et al., 2003). These authors suggested that narcolepsy is either associated with microscopic changes untractable by VBM or that functional abnormalities of hypocretin neurons are not associated with structural correlates (Overeem et al., 2003). In another VBM study, however, narcoleptic patients exhibited bilateral cortical gray-matter reductions predominantly in inferior temporal and inferior frontal brain regions (Kaufmann et al., 2002). Relative global gray-matter loss was independent of disease duration or medication history and there were no significant subcortical gray-matter alterations. Still another VBM study detected a significant bilateral decrease in hypothalamic gray-matter concentration in narcoleptic patients related to unaffected healthy controls (Draganski et al., 2002). Decreased gray-matter concentration was also observed in the vermis, the superior temporal gyrus, and the right nucleus accumbens. Given the major projection sites of hypocretin-1 (the hypothalamus among others) and hypocretin-2 (the nucleus accumbens among others), the decrease in gray matter was thought to reflect the secondary neuronal loss due to the destruction of specific hypocretin projections (Draganski et al., 2002). This study was corroborated by another VBM study (Buskova et al., 2006). Another VBM study found significant gray-matter loss in the right prefrontal and frontomesial cortex of patients with narcolepsy (Brenneis et al., 2005). For the authors, the volume reduction of gray matter in narcoleptic patients could indicate a disease-related atrophy.

Several factors can explain these controversial results, such as possible bias due to inhomogeneous patient groups, prestatistical image processing, or history of treatment (Brenneis et al., 2005). VBM studies with large sample of drug-naive patients should be performed to advance further in this very complex physiopathology.

Proton magnetic resonance spectroscopy (^{1}H-MRS) was used in order to assess the *N*-acetylaspartate (NAA) content in the ventral pontine areas (Ellis et al., 1998) and the hypothalamus of narcoleptic

patients (Lodi et al., 2004). In both studies, an analysis of spectral peak area ratios revealed a decrease in the NAA/creatine-phosphocreatine ratio in narcoleptic patients compared with control subjects. These results were interpreted as a neuronal loss or damage in the ventral pontine area and in the hypothalamus of the narcoleptic patients.

Another ^{1}H-MRS study in 17 narcoleptics patients showed a higher GABA concentration in the medial prefrontal cortex, which was more prominent in patients without nocturnal sleep disturbance (Kim et al., 2008). The authors suggest it might be a compensatory mechanism to reduce nocturnal sleep disturbances in narcolepsy.

The results of the Lodi study (Lodi et al., 2004) were confirmed by an [18]FDG PET study that was used to measure relative difference between CMRGlu of 24 narcoleptic patients and 24 normal controls during wakefulness (Joo et al., 2004) (Figure 6.4). Narcoleptic patients had reduced CMRGlu in bilateral precuneus, bilateral posterior hypothalami, and mediodorsal thalamic nuclei (Joo et al., 2004). This study prevails over a SPECT study that was subsequently conducted (Yeon Joo et al., 2005).

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper-airway obstruction that occur during sleep, generally associated with a reduction in blood oxygen saturation (AASM, 2001). Population-based epidemiologic studies revealed a high prevalence (1–5% of adult men) of OSAS. These studies also associate OSAS with significant morbidity, such as hypertension, cardiovascular disease, stroke, or motor vehicle accidents (Young et al., 2002).

OSAS has a complex pathophysiology which is not yet completely understood. Several studies suggest that OSAS in all age groups is due to a combination of both anatomic airway narrowing and abnormal upper-airway neuromotor tone. Besides the known anatomic factors, such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy, that contribute to OSAS, clear anatomical contributing factors cannot always be identified (AASM, 2001). This suggests that alterations in upper-airway neuromuscular tone also play an important role in the etiology of OSAS (Arens and Marcus, 2004). The pathophysiology of OSAS also includes enhanced chemoreflex sensitivity and an exaggerated sympathetic response during hypoxemic episodes (Caples et al., 2005). Furthemore, it is still a matter of debate whether the cognitive consequences of OSAS are reversible or not (Aloia et al., 2004; Brown, 2005). Functional impairments are often associated with neuropsychological deficits which are often thought to be reversible with appropriate treatment (Aloia et al., 2004; Brown, 2005). In contrast, structural alterations may indicate irreversible cerebral changes and would underpin permanent cognitive impairments (Alchanatis et al., 2004), although this proposal remains a matter of debate in the literature (Gale and Hopkins, 2004). In addition, the specific consequences of sleep fragmentation and hypoxia on cognition and brain function have still to be teased apart and thoroughly characterized.

We will present successively an overview of cognitive alterations, changes in brain structure and function, and finally neuroimaging studies exploring ventilatory control in OSAS.

OVERVIEW OF COGNITIVE ALTERATIONS

Alterations of mental process, behavior, and interpersonal relations are a common observation in OSAS patients (Brown, 2005). Moreover OSAS has been associated with distinct cognitive alterations in various
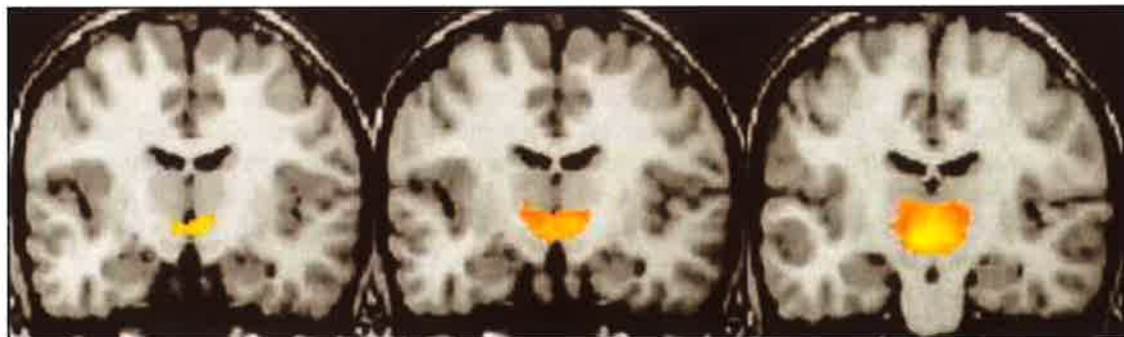
Fig. 6.4. Cerebral glucose metabolism (CMRGlu) in the hypothalamus and thalamus in narcoleptic patients during wakefulness.

Bilateral posterior hypothalami and mediodorsolateral thalamic nuclei show hypometabolism in narcoleptic patients compared to controls. (Reproduced with permission from Joo et al. (2004), Copyright 2004. Wiley-Liss, Inc., A Wiley Company.)

domains. Both fragmented sleep and hypoxemia are proposed as the main factors leading to neurocognitive impairment during wakefulness (Berry et al., 1986; Findley et al., 1986, 1995; Bedard et al., 1991; Cheshire et al., 1992; Bonnet, 1993; George et al., 1996; Young et al., 1997). Several studies emphasized the deterioration of executive functions in OSAS patients, including the inability to initiate new mental processes (Naegele et al., 1995; Feuerstein et al., 1997), deficits in working memory (Greenberg et al., 1987; Naegele et al., 1995), contextual memory (Harrison et al., 2000), selective attention (Kotterba et al., 1998), continuous attention (Kotterba et al., 1998), and analysis and synthesis (Greenberg et al., 1987; Naegele et al., 1995). A 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 (Beebe et al., 2003). In addition, a "cognitive reserve" could be protective against OSAS-related cognitive decline (Alchanatis et al., 2005). Most studies suggest that cognitive impairments improve with nasal continuous positive airway pressure (nCPAP) treatment but evidence suggests that some changes may be permanent (Aloia et al., 2004; Brown, 2005). For instance, after nCPAP, OSAS patients improved attention / vigilance in most studies and did not improve constructional abilities or psychomotor functioning (Aloia et al., 2004). Intrinsic neural dysfunction related to these deleterious factors would add to daytime sleepiness to explain the neuropsychological deterioration of OSAS patients (Beebe and Gozal, 2002).

Interestingly, several studies have linked OSAS and depression (Schroder and O'Hara, 2005). Moreover, several authors have demonstrated improvement in depression scores and overall psychopathology by using nCPAP therapy (Engleman et al., 1997).

STRUCTURAL CHANGES

Using VBM in 21 patients with OSAS and in 21 control subjects, structural changes in brain morphology were assessed (Macey et al., 2002). Diminished regional and often unilateral 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 cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum. Another VBM study conducted in 7 OSAS patients and 7 controls showed a significantly lower gray-matter concentration solely within the left hippocampus in the OSAS patients (Morrell et al., 2003). There was no difference in total gray-matter volume between the two groups. In

a more recent VBM study (27 OSAS patients and 24 controls), it has been found that there are no gray-matter volume deficits or focal structural changes in severe OSAS patients. Whole-brain volume decreases without focal changes after 6 months of cPAP treatment (O'Donoghue et al., 2005).

Another study compared both neuropathological and neuropsychological effects of hypoxia in patients with either carbon monoxide poisoning or OSAS (Gale and Hopkins, 2004). Brain imaging showed a hippocampal atrophy in both groups even though a linear relationship between hippocampal volume and memory performance was found for only a subset of selected tests (the delayed recall or the Rey–Osterrieth Complex Figure Design and Trial 6 of the Rey Auditory Verbal Learning Test, among others), and only in the OSAS group. Hippocampal volume was related to performance on nonverbal information processing (Wechsler Adult Intelligence Scale – Revised Block Design). Further data will be necessary to delineate better the specificity and contribution of hippocampal atrophy in OSAS.

CHANGES IN BRAIN FUNCTION

As described earlier, cognitive executive functions, associated with specific prefrontal-subcortical brain circuits, are dysfunctional in OSAS patients (Alchanatis et al., 2004). Another study, using single-voxel ^{1}H-MRS, attempted to demonstrate that OSAS can induce axonal loss or dysfunction and myelin metabolism impairment in the frontal periventricular white matter. Magnetic resonance spectra were obtained from prefrontal cortex, parieto-occipital and frontal periventricular white matter. NAA-to-creatine and choline-to-creatine ratios were significantly lower in the frontal white matter of OSAS patients when compared to controls. Absolute concentrations of NAA and choline were also significantly reduced in the frontal white matter of OSAS patients (Alchanatis et al., 2004). These findings may offer an explanation for the sometimes irreversible cognitive deficits associated with OSAS. Despite these results, which suggest an implication of frontal-lobe white-matter lesion in daytime cognitive dysfunction, it still lacks a direct relationship between frontal dysfunction and cognitive impairments. Likewise, some clarification is needed to show the respective roles (in cognitive alterations supposed to be frontal) of hypoxia, sleep fragmentation, or sleep deprivation which occur during OSAS.

Another ^{1}H-MRS study in OSAS patients showed that, in the left hippocampal area, the N-acetyl-containing/creatine-containing compounds ratio was significantly increased (Bartlett et al., 2004). Analysis indicated that this was probably due to a decrease in creatine-containing

compounds which was correlated with worse OSAS severity and neurocognitive performance. Authors suggest that the metabolic changes in the hippocampal area represent adjustments to brain bioenergetics and may reflect the different susceptibility of this tissue to hypoxic damage in OSAS, as in ischemic preconditioning. An earlier and less reflective ^{1}H-MRS study in 23 OSAS patients showed that the NAA-to-choline ratio in cerebral white matter was significantly lower in patients with moderate to severe OSAS than in patients with mild OSAS and healthy subjects (Kamba et al., 1997). This finding suggests the presence of cerebral damage, probably caused by repeated apneic episodes. In addition, a study by Halbower et al. (2006) showed a decrease in the NAA-to-choline 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 nCPAP treatment. An early ^{99}mTC-HMPAO SPECT study in 14 adult OSAS patients (Ficker et al., 1997) reported a marked frontal hyperperfusion in 5 patients. In distinction, regional analysis showed a reduced perfusion in the left parietal region. It is noteworthy that all these changes were completely reversed by effective nCPAP therapy, suggesting that the main deleterious effects of OSAS on brain activity are reversible. The authors suggest that 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. Using ^{1}H-MRS, a study showed that NAA in the parietal-occipital cortex was significantly reduced more in 14 OSAS patients than in controls, but this reduction persisted after nCPAP therapy despite clinical, neuropsychological, and neurophysiological normalization (Tonon et al., 2007). In addition, 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 (Hashimoto et al., 2006). Simultaneously, the subjective effects of this treatment were assessed by a visual analog scale and confirmed successful reduction of respiratory stress.

CHANGES IN VENTILATORY CONTROL

In OSAS patients, apnea has considerable hemodynamic consequences that are mediated by a complex cascade of physiological events. Repetitive episodes of apnea trigger marked fluctuations in both blood pressure and heart rate, with consequent effects on the estimates of cardiovascular variability (Kryger et al., 2000). 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 (Mateika and Ellythy, 2003). For instance, the ventilatory response to carbon dioxide is elevated in OSAS patients (Mateika and Ellythy, 2003). The partial pressure of carbon dioxide that delimits the carbon dioxide ventilatory recruitment threshold is elevated in patients with OSAS (Mateika and Ellythy, 2003). 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 (Harper et al., 2003; Henderson et al., 2003; Macey et al., 2003, 2006). For instance, altered neuronal response after Valsalva maneuver was shown in cerebellar, limbic, and motor areas involved in the control of diaphragmatic and upper-airway muscles (Figure 6.5). Enhanced sympathetic outflow after a forehead cold pressor challenge results in both diminished and exaggerated responses in limbic area, cerebellar, frontal cortex, and thalamus.

An fMRI study evaluated the brain activity changes during baseline and expiratory loading conditions in 9 OSAS patients and 16 controls (Macey et al., 2003). Reduced neural signals emerged in OSAS patients within the frontal cortex, anterior cingulate, cerebellar dentate nucleus, dorsal pons, anterior insula, and lentiform nuclei. Signal increases in OSAS over control subjects developed in the dorsal midbrain, hippocampus, quadrangular cerebellar lobule, ventral midbrain, and ventral pons. Fastigial nuclei and the amygdala showed substantially increased variability in OSAS subjects. No group differences were found in the thalamus. Both groups developed similar expiratory loading pressures, but appropriate autonomic responses did not emerge in OSAS patients. A more recent fMRI study evaluated the brain activity changes during baseline and inspiratory loading in 7 OSAS patients and 11 controls (Macey et al., 2006). A number of cortical and subcortical areas mediating sensory and autonomic processes, and motor timing were affected. Altered signals appeared in primary sensory thalamus and sensory cortex, supplementary motor cortex, cerebellar cortex and deep nuclei, cingulate, medial temporal, and insular cortices, right hippocampus, and midbrain (Macey et al., 2006).

These altered brain activation patterns, during waking, could reflect neural dysfunctions that mediate
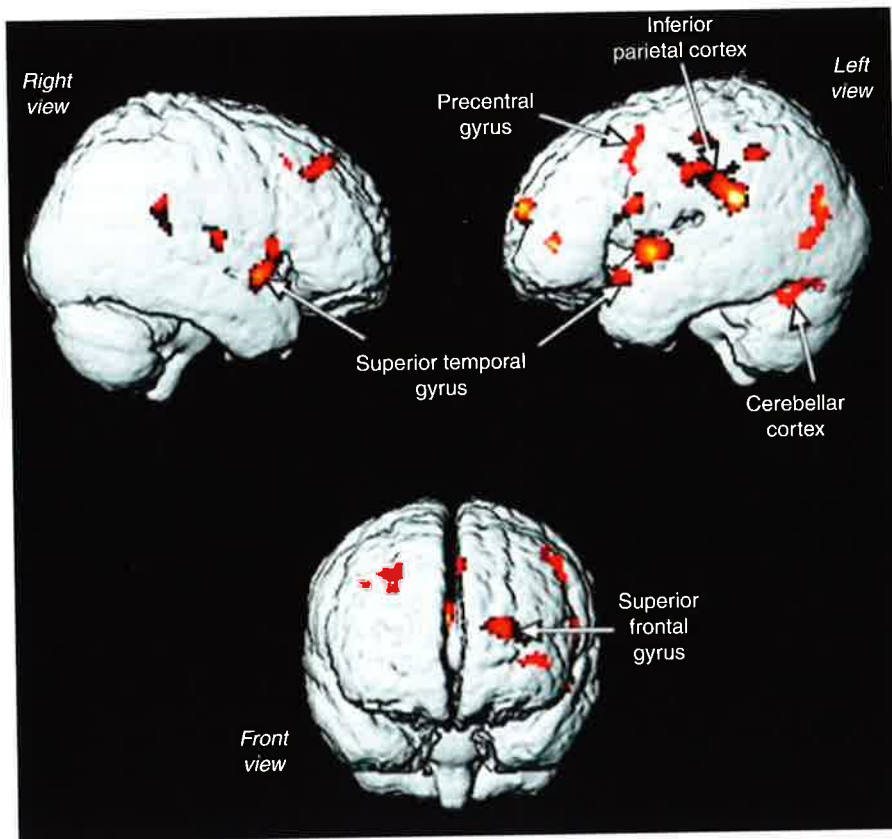
Fig. 6.5. Neural response (cerebral blood flow) during Valsalva maneuvers in obstructive sleep apnea syndrome using functional magnetic resonance imaging.

There are areas of significant difference in signal intensity between controls and obstructive sleep apnea syndrome (OSAS) patients during Valsalva maneuver in cortical regions. Voxels are color-coded for depth from the surface and rendered on to the cortex of an average anatomical image set of all control and OSAS patients. (Reproduced from Henderson et al. (2003), with permission from the Journal of Applied Physiology, Copyright 2003. American Physiological Society.)

the prominently diminished upper-airway tone which occurs in OSAS patients during sleep.

SUMMARY

Altogether, these findings suggest that neuropsychological damage in OSAS is brought about by various alterations in prefrontal cortex, hippocampal and parietal cortex. Even if abnormal brain activations are reversible under nCPAP, several studies have suggested that not all neuropsychological damage disappears after nCPAP (Bedard et al., 1993; Feuerstein et al., 1997; Naegele et al., 1998). Accordingly, structural brain changes have been reported in OSAS patients. Although the basic pathophysiological mechanisms are not completely understood, a dysregulation in the autonomic regulation seems to have an important role in these mechanisms. However, it is important to notice that peripheral factors may confound the deficits observed in studies focused on OSAS patients, including exaggerated body mass index and

motivational problems (Tasali and Van Cauter, 2002; Spiegel et al., 2004).

Abnormal motor behaviors during sleep

Abnormal motor behaviors during sleep include the periodic limb movements and RBD, a specific parasomnia syndrome associated with REM sleep. Abnormal motor behaviors are a common cause of sleep disturbance and the understanding of the underlying physiopathology should be useful in the management (diagnostic and prognostic information) of insomnia (Montplaisir et al., 1994).

PERIODIC LIMB MOVEMENTS

Periodic limb movement disorder during sleep (PLMS) and RLS are distinct but overlapping syndromes. PLMS is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep (ASDA, 1990). RLS is a disorder

characterized by uncomfortable leg sensations, usually prior to sleep onset, that cause an almost irresistible urge to move the legs (ASDA, 1990).

The diagnosis of PLMS requires the presence of PLMS on polysomnography as well as an associated sleep complaint. RLS, however, is essentially made on clinical grounds. Moreover, PLMS are themselves non-specific, occurring both with RLS and with other sleep disorders (e.g., narcolepsy, sleep apnea syndrome, RBD) as well as in normal individuals (Tan and Ondo, 2000). Thus, the diagnosis of PLMS requires the exclusion of other potential causes for the associated sleep complaint (Lesage and Hening, 2004).

Structural cerebral abnormalities have been reported in patients with idiopathic RLS (Etgen et al., 2005). 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 (Bucher et al., 1997). The leg discomfort 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 brainstem close to the reticular formation. Interestingly, when subjects were asked to imitate PLMS voluntarily, there was no activation in the brainstem, 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. In addition, a recent VBM study examining 14 patients with idiopathic RLS detected a slightly increased gray-matter density in the ventral hippocampus and in the middle orbitofrontal gyrus (Hornyak et al., 2007).

Recently, 45 idiopathic RLS patients and 30 healthy controls were studied using quantitative whole-brain-based diffusion tensor imaging (Unrath et al., 2008). In the RLS group, regional fractional anisotropy used as a quantitative marker of white-matter integrity was reduced in several subcortical areas, including areas in the proximity of motor and somatosensory cortices, the right hemispheric thalamus (posterior ventral lateral nucleus), in motor projectional fibers, and adjacent to the left anterior cingulum. In addition, high-resolution three-dimensional MRI was performed in 63 idiopathic RLS patients using optimized VBM (Unrath et al.,

2007). As compared to controls, regional decreases of gray-matter volume were shown in primary somatosensory cortex and primary motor areas. Clusters in both areas correlated with the severity of RLS symptoms and with disease duration. Together these results show a neocortical and subcortical network of area involving sensorimotor impairment. Incongruent results might be due to differences in populations examined, such as treatment-induced effects on cerebral morphology in RLS, duration of the illness, or methodological issues (size of the samples).

A suprasegmental release of inhibition of descending inhibitory pathways implicating dopaminergic, adrenergic, and opiate systems is thought to be involved in PLMS pathogenesis (Wetter and Pollmacher, 1997). This is supported by the observation of PLMS during spinal anaesthesia (Watanabe et al., 1987), for instance. Patients' condition worsens when dopamine antagonists are given (Akpinar, 1982), whereas dopaminergic drugs have been shown to relieve PLMS (Brodeur et al., 1988; Montplaisir et al., 1991, 2000). Staedt et al. have tested the hypothesis of decreased dopaminergic activity in PLMS patients. In a series of SPECT studies, they report a decreased IBZM striatal uptake, indicating a lower D2 receptor occupancy in PLMS patients (Staedt et al., 1993, 1995a, b; Happe et al., 2003). Treating patients with dopamine replacement therapy increased the IBZM binding and improved the sleep quality in these patients (Staedt et al., 1995a).

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 3 beta-(4-iodophenyl) tropane-2 beta-carboxylate (^{123}I beta-CIT), a ligand of dopamine transporter, and ^{123}I-IBZM SPECT respectively (Michaud et al., 2002). There was no difference in DA transporter (^{123}I-beta-CIT) binding between RLS-PLMS patients and controls. The study of the striatal D2 receptor binding (^{123}I-IBZM) revealed again a significantly lower binding in patients as compared with controls. Numerous mechanisms may be responsible for this decrease in D2 receptor binding. Since ^{123}I-beta-CIT binding is normal, a decreased number of D2 receptors or a decreased affinity of D2 receptors for ^{123}I-IBZM is more likely than a downregulation of D2 receptors due to an increased level of synaptic dopamine (Michaud et al., 2002).

Fourteen patients with idiopathic RLS and PLMS successfully treated by dopaminergic (e.g., ropinirole) and nondopaminergic (e.g., gabapentin) treatment were investigated while off medication by using ^{123}I-IBZM and SPECT (Tribl et al., 2004). They were compared to 10 healthy sex- and age-matched control subjects. The patients presented with sleep disturbances, severe

PLMS, and severe RLS symptoms during the period of scanning while off medication and did not show any significant differences in striatal to frontal ^{123}I-IBZM binding to D2 receptors compared to controls, in contrast to the previous study. The authors suggest that the dopaminergic system in these patients might be affected elsewhere, possibly in the diencephalospinal part of the dopaminergic system (Tribl et al., 2004).

These studies support the hypothesis that a central dopamine dysfunction is involved in the physiopathology of RLS-PLMS, although more recent studies specifically implicate the cerebral metabolism of iron (Allen, 2004). 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 D2 receptors (Kryger et al., 2000).

A neuropathologic study (7 RLS brain and 5 normal brain) has shown a marked decrease in H-ferritin (ferritin heavy chain) and iron staining in RLS subtantia nigra. Transferrin receptor staining on neuromelanin-containing cells was decreased in RLS brains compared to normal brains, whereas transferrin staining in these cells was increased (Connor et al., 2003). Using a special MRI measurement (R_2^*), Allen et al. (2001) assessed regional brain iron concentrations in 10 subjects (5 with RLS, 5 controls). R_2^* was significantly decreased in the substantia nigra, and somewhat less significantly in the putamen, both in proportion to RLS severity. These results show that this R_2^* MRI measurement may prove useful in the management of RLS, and also indicate that brain iron insufficiency may occur in RLS patients in some brain regions. In addition, another study found diminished iron concentration across 10 brain regions in early-onset RLS but not in late-onset RLS when compared to controls (Earley et al., 2006).

These convergent observations seem to show that RLS may be a functional disorder resulting from impaired iron metabolism (i.e., impaired regulation of transferring receptors) (Connor et al., 2003). Interestingly, altered iron metabolism in lymphocytes was shown in 24 subjects with RLS as compared with controls. Lymphocytes showed an increase in ferroportin (a transmembrane protein that transports iron from the inside to the outside of a cell), implying increased cellular iron excretion, in the face of increased iron need (Earley et al., 2008).

REM SLEEP BEHAVIOR DISORDER

RBD is characterized by brisk movements of the body associated with dream mentation that usually disturbs sleep continuity (Schenck et al., 1986). During the nocturnal spells, patients behave as if they are acting out their dream (ASDA, 1997). This disease may be idiopathic (up to 60%) or associated with other neurologic disorders. A sizeable proportion of patients with RBD will develop extrapyramidal disorders (Schenck et al., 1996; Gagnon et al., 2002, 2004), Lewy body dementia (Fantini et al., 2005), and multiple system atrophy (Plazzi et al., 1997; Gilman et al., 2003). More recently, a strong association between RBD and alpha-synucleinopathies has been observed, with the parasomnia often preceding the clinical onset of the neurodegenerative disease (Fantini et al., 2005; Boeve et al., 2007).

Worthy of note, lesions in the mesopontine tegmentum of cats can lead to the disappearance of muscle atonia during REM sleep together with dream enactment behavior (Sakai et al., 1979).

A study combining MRI and ^{123}I-IMP SPECT in 20 RBD patients 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 (Shirakawa et al., 2002). Another SPECT study in 8 RBD patients during waking rest showed decreased activity in frontal and temporoparietal cortices but found increased activity in the pons, putamen, and right hippocampus (Mazza et al., 2006). In addition, brainstem function was evaluated by ^{1}H-MRS in a 69-year-old man with idiopathic RBD. An analysis of spectral peak area ratios revealed an increase in the choline/creatine ratio. This change suggests that brainstem neurons have functional impairment at the cell membrane level (Miyamoto et al., 2000). In contrast, one group using ^{1}H-MRS in 15 patients with idiopathic RBD and 15 matched control subjects failed to reveal any difference in metabolic peaks of NAA/creatine, choline/creatine and myoinositol/creatine ratios in the pontine tegmentum and the midbrain (Iranzo et al., 2002). This result does not support the hypothesis of marked mesopontine neuronal loss or ^{1}H-MRS detectable metabolic disturbances in idiopathic RBD. Despite these equivocal results, ^{1}H-MRS may provide for noninvasive metabolic evaluation of brainstem neuronal function in RBD and find application in the differentiation of secondary RBD with neurodegenerative disorders from idiopathic disorders.

Using SPECT and (N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane labeled with iodine-123 (IPT), a ligand of striatal presynaptic dopamine transporters), IPT binding in RBD patients ($n = 5$) during wakefulness was found to be lower than in normal controls but higher than in Parkinson patients ($n = 14$) (Eisensehr et al., 2000, 2003b). These results suggest that the number of presynaptic dopamine transporters is decreased in both Parkinson 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 dopamine 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 (Albin et al., 2000). Likewise ^{11}C-DTBZ binding in the striatum was decreased in 13 patients with multiple-system atrophy (MSA) (Gilman et al., 2003). 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 these alterations play a causal role in the pathophysiology of RBD or reflect functional consequences and adaptations to the pathological conditions. Although there is evidence that some Parkinson patients do show excessive nocturnal movements (Trenkwalder, 1998; Happe et al., 2003), it is interesting that only a small percentage of Parkinson patients develop full-blown RBD. This suggests that modifications of other systems of neurotransmission are probably necessary for full-blown RBD to occur.

CONCLUSIONS

Brain functional imaging provides unprecedented possibilities to explore brain function during normal and pathological sleep. Nevertheless, brain functional imaging in sleep is still in its infancy, at present mostly restricted to research purposes.

As shown in this review, brain functional imaging in patients affected by sleep disorders may address different kinds of issues. The first topic is the characterization of the cerebral aftermath of sleep disruption due to intrinsic sleep disorders or to extrinsic environmental or medical causes.

The second, more ambitious, aim would be to characterize better the primary physiopathological mechanisms of sleep disorders, or at least their cerebral correlates. This attempt is hampered by several factors. Scanning patients during their sleep is not at all easy, for practical and methodological reasons. It requires some adjustment in the imaging environment and it is never guaranteed that the participant will sleep during data acquisition opportunities. Clinical manifestations in sleep disorders are often unpredictable and transient (e.g., sleepwalking, RBD); thus one cannot predict whether the pathological event will occur during the scanning period. In the same manner, most clinical manifestations induce large movements. These pathological movements during sleep may lead to image artifacts and misinterpretation of brain activation, making their study in functional neuroimaging very difficult. In this respect, SPECT is probably the most appropriate procedure for the reason that the radiotracer can be simply administered during the clinical events, well before the brain images are acquired. A example of such a study pertains to sleepwalking (Bassetti et al., 2000). Finally, and not least, the theoretical framework necessary for designing the protocol of clinical neuroimaging studies is not necessarily available for all sleep disorders. For instance, the discovery of the hypocretin system and its role in narcolepsy in the late 1990s (Lin et al., 1999) has indubitably changed how experimental designs should be run in neuroimaging in narcoleptic patients. Nevertheless, alternative approaches are available, as the functional and structural consequences of these sleep disorders can also be assessed during wakefulness, as seen above.

A third area of interest is the establishment of a 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 the clinical observation.

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

Although substantial progress in methodology has been made, a large research effort is still needed to characterize better pathophysiological mechanisms of sleep disorders, teasing apart their causes from their consequences. Optimally, brain functional imaging should be helpful in order to assess, in an individual patient, the functional and structural consequences of long-term sleep disruption.

These considerations argue for closer collaboration and partnership between basic neuroscientist sleep researchers, sleep clinicians, and neuroimagers in designing and conducting more informative (multimodal) experiments in a large number of sleep disorders.

ACKNOWLEDGMENTS

REFERENCES

AASM (2001). International Classification of Sleep Disorders. Diagnostic and Coding Manual. American Academy of Sleep Medicine, Chicago, IL.

Akpinar S (1982). Treatment of restless legs syndrome with levodopa plus benserazide. Arch Neurol 39 (11): 739.

Albin RL, Koeppe RA, Chervin RD et al. (2000). Decreased striatal dopaminergic innervation in REM sleep behavior disorder. Neurology 55 (9): 1410–1412.

Alchanatis M, Deligiorgis N, Zias N et al. (2004). Frontal brain lobe impairment in obstructive sleep apnoea: a proton MR spectroscopy study. Eur Respir J 24 (6): 980–986.

Alchanatis M, Zias N, Deligiorgis N et al. (2005). Sleep apnea-related cognitive deficits and intelligence: an implication of cognitive reserve theory. J Sleep Res 14 (1): 69–75.

Aldrich MS, Hollingsworth Z, Penney JB et al. (1992). Dopamine-receptor autoradiography of human narcoleptic brain. Neurology 42 (2): 410–415.

Allen R (2004). Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med 5 (4): 385–391.

Allen RP, Barker PB, Wehrl F et al. (2001). MRI measurement of brain iron in patients with restless legs syndrome. Neurology 56 (2): 263–265.

Aloia MS, Arnedt JT, Davis JD et al. (2004). Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc 10 (5): 772–785.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). APA Press, Washington DC.

Andersson JL, Onoe H, Hetta J et al. (1998). Brain networks affected by synchronized sleep visualized by positron emission tomography. J Cereb Blood Flow Metab 18 (7): 701–715.

Arens R, Marcus CL (2004). Pathophysiology of upper airway obstruction: a developmental perspective. Sleep 27 (5): 997–1019.

Aron AR, Robbins TW, Poldrack RA et al. (2004). Inhibition and the right inferior frontal cortex. Trends Cogn Sci 8 (4): 170–177.

ASDA (1990). International Classification of Sleep Disorders. Diagnostic and Coding Manual. American Sleep Disorders Association, Rochester, MN.

ASDA (1997). International Classification of Sleep Disorders and Codign Manual. American Sleep Disorders Association, Rochester, MN.

Asenbaum S, Zeithofer J, Saletu B et al. (1995). Technetium-99m-HMPAO SPECT imaging of cerebral blood flow during REM sleep in narcoleptics. J Nucl Med 36 (7): 1150–1155.

Ashburner J, Friston KJ (2000). Voxel-based morphometry – the methods. Neuroimage 11 (6 Pt 1): 805–821.

Ashburner J, Friston KJ (2001). Why voxel-based morphometry should be used. Neuroimage 14 (6): 1238–1243.

Bartlett DJ, Rae C, Thompson CH et al. (2004). Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. Sleep Med 5 (6): 593–596.

Bassetti C, Vella S, Donati F et al. (2000). SPECT during sleepwalking. Lancet 356 (9228): 484–485.

Baumann CR, Bassetti CL (2005). Hypocretins (orexins): clinical impact of the discovery of a neurotransmitter. Sleep Med Rev 9 (4): 253–268.

Bedard MA, Montplaisir J, Richer F et al. (1991). Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol 13 (6): 950–964.

Bedard MA, Montplaisir J, Malo J et al. (1993). Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 15 (2): 330–341.

Beebe DW, Gozal D (2002). Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 11 (1): 1–16.

Beebe DW, Groesz L, Wells C et al. (2003). The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 26 (3): 298–307.

Benca RM (2000). Mood disorders. In: MH Kryger, T Roth, WC Dement (Eds.), Principles and Practice of Sleep Medicine. Elsevier, Saunders, pp. 1040–1057.

Berry DT, Webb WB, Block AJ et al. (1986). Nocturnal hypoxia and neuropsychological variables. J Clin Exp Neuropsychol 8 (3): 229–238.

Boeve BF, Silber MH, Saper CB et al. (2007). Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 130 (Pt 11): 2770–2788.

Bonnet MH (1993). Cognitive effects of sleep and sleep fragmentation. Sleep 16 (8 Suppl): S65–S67.

Bonnet MH, Arand DL (1995). 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep 18 (7): 581–588.

Bonnet MH, Arand DL (1997). Hyperarousal and insomnia. Sleep Med Rev 1 (2): 97–108.

Borbely AA (2001). From slow waves to sleep homeostasis: new perspectives. Arch Ital Biol 139 (1–2): 53–61.

Born AP, Law I, Lund TE et al. (2002). Cortical deactivation induced by visual stimulation in human slow-wave sleep. Neuroimage 17 (3): 1325–1335.

Bouhuys AL, van den Burg W, van den Hoofdakker RH et al. (1995). The relationship between tiredness prior to sleep deprivation and the antidepressant response to sleep deprivation in depression. Biol Psychiatry 37 (7): 457–461.

Braun AR, Balkin TJ, Wesenten NJ et al. (1997). Regional cerebral blood flow throughout the sleep–wake cycle. An H2(15)O PET study. Brain 120 (Pt 7): 1173–1197.

Braun AR, Balkin TJ, Wesensten NJ et al. (1998). Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 279 (5347): 91–95.

Brenneis C, Brandauer E, Frauscher B et al. (2005). Voxel-based morphometry in narcolepsy. Sleep Med 6: 531–536.

Brodeur C, Montplaisir J, Godbout R et al. (1988). Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. Neurology 38 (12): 1845–1848.

Brown WD (2005). The psychosocial aspects of obstructive sleep apnea. Semin Respir Crit Care Med 26 (1): 33–43.

Bucher SF, Seelos KC, Oertel WH et al. (1997). Cerebral generators involved in the pathogenesis of the restless legs syndrome. Ann Neurol 41 (5): 639–645.

Buskova J, Vaneckova M, Sonka K et al. (2006). Reduced hypothalamic gray matter in narcolepsy with cataplexy. Neuro Endocrinol Lett 27 (6): 769–772.

Buysse DJ, Tu XM, Cherry CR et al. (1999). Pretreatment REM sleep and subjective sleep quality distinguish depressed psychotherapy remitters and nonremitters. Biol Psychiatry 45 (2): 205–213.

Buzsaki G (1998). Memory consolidation during sleep: a neurophysiological perspective. J Sleep Res 7 (Suppl 1): 17–23.

Calvo JM, Badillo S, Morales-Ramirez M et al. (1987). The role of the temporal lobe amygdala in ponto-geniculo-occipital activity and sleep organization in cats. Brain Res 403 (1): 22–30.

Calvo JM, Simon-Arceo K, Fernandez-Mas R et al. (1996). Prolonged enhancement of REM sleep produced by carbachol microinjection into the amygdala. Neuroreport 7 (2): 577–580.

Caples SM, Gami AS, Somers VK et al. (2005). Obstructive sleep apnea. Ann Intern Med 142 (3): 187–197.

Chabas D, Habert MO, Maksud P et al. (2007). Functional imaging of cataplexy during status cataplecticus. Sleep 30 (2): 153–156.

Chee MW, Chuah LY (2008). Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. Curr Opin Neurol 21 (4): 417–423.

Cheshire K, Engleman H, Deary I et al. (1992). Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 152 (3): 538–541.

Clark LA, Watson D (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol 100 (3): 316–336.

Clark CP, Frank LR, Brown GG et al. (2001). Sleep deprivation, EEG, and functional MRI in depression: preliminary results. Neuropsychopharmacology 25 (5 Suppl): S79–S84.

Connor JR, Boyer PJ, Menzies SL et al. (2003). Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 61 (3): 304–309.

Czisch M, Wetter TC, Kaufmann C et al. (2002). Altered processing of acoustic stimuli during sleep: reduced auditory activation and visual deactivation detected by a combined fMRI/EEG study. Neuroimage 16 (1): 251–258.

Czisch M, Wehrle R, Kaufmann C et al. (2004). Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. Eur J Neurosci 20 (2): 566–574.

Dang-Vu TT, Desseilles M, Albouy G et al. (2005). Dreaming: a neuroimaging view. Swiss Archives of Neurology and Psychiatry 156 (8): 415–425.

Dang-Vu TT, Schabus M, Desseilles M et al. (2008). Spontaneous neural activity during human slow wave sleep: an EEG/fMRI study. Proc Natl Acad Sci U S A 105: 15160–15165.

Datta S, Siwek DF, Patterson EH et al. (1998). Localization of pontine PGO wave generation sites and their anatomical projections in the rat. Synapse 30 (4): 409–423.

Draganski B, Geisler P, Hajak G et al. (2002). Hypothalamic gray matter changes in narcoleptic patients. Nat Med 8 (11): 1186–1188.

Drevets WC (2000). Neuroimaging studies of mood disorders. Biol Psychiatry 48 (8): 813–829.

Drevets WC (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11 (2): 240–249.

Drouot X, Moutereau S, Nguyen JP et al. (2003). Low levels of ventricular CSF orexin/hypocretin in advanced PD. Neurology 61 (4): 540–543.

Earley CJBBP, Horska A, Allen RP et al. (2006). MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Med 7 (5): 458–461.

Earley CJ, Ponnuru P, Wang X et al. (2008). Altered iron metabolism in lymphocytes from subjects with restless legs syndrome. Sleep 31 (6): 847–852.

Ebert D, Feistel H, Barocka A et al. (1991). Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tc-99m-HMPAO SPECT. Psychiatry Res 40 (4): 247–251.

Ebert D, Feistel H, Barocka A et al. (1994a). Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation–preliminary results. Biol Psychiatry 35 (11): 880–885.

Ebert D, Feistel H, Kaschka W et al. (1994b). Increased limbic blood flow and total sleep deprivation in major depression with melancholia. Psychiatry Res 55 (2): 101–109.

Eisensehr I, Linke R, Noachtar S et al. (2000). Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. Brain 123 (Pt 6): 1155–1160.

Eisensehr I, Linke R, Tatsch K et al. (2003a). Alteration of the striatal dopaminergic system in human narcolepsy. Neurology 60 (11): 1817–1819.

Eisensehr I, Linke R, Tatsch K et al. (2003b). Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. Sleep 26 (5): 507–512.

Ellis CM, Simmons A, Lemmens G et al. (1998). Proton spectroscopy in the narcoleptic syndrome. Is there evidence of a brainstem lesion? Neurology 50 (2 Suppl 1): S23–S26.

Ellis CM, Monk C, Simmons A et al. (1999). Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Actions of modafinil. J Sleep Res 8 (2): 85–93.

Engleman HM, Martin SE, Deary IJ et al. (1997). Effect of CPAP therapy on daytime function in patients with

mild sleep apnoea/hypopnoea syndrome. Thorax 52 (2): 114–119.

Etgen T, Draganski B, Ilg C et al. (2005). Bilateral thalamic gray matter changes in patients with restless legs syndrome. Neuroimage 24 (4): 1242–1247.

Fantini ML, Ferini-Strambi L, Montplaisir J et al. (2005). Idiopathic REM sleep behavior disorder: toward a better nosologic definition. Neurology 64 (5): 780–786.

Feuerstein C, Naegele B, Pepin JL et al. (1997). Frontal lobe-related cognitive functions in patients with sleep apnea syndrome before and after treatment. Acta Neurol Belg 97 (2): 96–107.

Ficker JH, Feistel H, Moller C et al. (1997). Changes in regional CNS perfusion in obstructive sleep apnea syndrome: initial SPECT studies with injected nocturnal 99mtc-HMPAO]. Pneumologie 51 (9): 926–930.

Findley LJ, Barth JT, Powers DC et al. (1986). Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. Chest 90 (5): 686–690.

Findley L, Unverzagt M, Guchu R et al. (1995). Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. Chest 108 (3): 619–624.

Finelli LA, Borbely AA, Achermann P et al. (2001). Functional topography of the human nonrem sleep electroencephalogram. Eur J Neurosci 13 (12): 2282–2290.

Gagnon JF, Bedard MA, Fantini ML et al. (2002). REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59 (4): 585–589.

Gagnon JF, Fantini ML, Bedard MA et al. (2004). Association between waking EEG slowing and REM sleep behavior disorder in PD without dementia. Neurology 62 (3): 401–406.

Gale SD, Hopkins RO (2004). Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. J Int Neuropsychol Soc 10 (1): 60–71.

George CF, Boudreau AC, Smiley A et al. (1996). Simulated driving performance in patients with obstructive sleep apnea. Am J Respir Crit Care Med 154 (1): 175–181.

Germain A, Buysse DJ, Wood A et al. (2004a). Functional neuroanatomical correlates of eye movements during rapid eye movement sleep in depressed patients. Psychiatry Res 130 (3): 259–268.

Germain A, Nofzinger EA, Kupfer DJ et al. (2004b). Neurobiology of non-REM sleep in depression: further evidence for hypofrontality and thalamic dysregulation. Am J Psychiatry 161 (10): 1856–1863.

Gilman S, Koeppe RA, Chervin RD et al. (2003). REM sleep behavior disorder is related to striatal monoaminergic deficit in MSA. Neurology 61 (1): 29–34.

Greenberg GD, Watson RK, Deptula D et al. (1987). Neuropsychological dysfunction in sleep apnea. Sleep 10 (3): 254–262.

Halbower AC, Degaonkar M, Barker PB et al. (2006). Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med 3 (8): e301.

Happe S, Pirker W, Klosch G et al. (2003). Periodic leg movements in patients with Parkinson's disease are associated with reduced striatal dopamine transporter binding. J Neurol 250 (1): 83–86.

Harper RM, Macey PM, Henderson LA et al. (2003). fMRI responses to cold pressor challenges in control and obstructive sleep apnea subjects. J Appl Physiol 94 (4): 1583–1595.

Harrison Y, Horne JA (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. J Sleep Res 7 (2): 95–100.

Harrison Y, Horne JA (1999). One night of sleep loss impairs innovative thinking and flexible decision making. Organ Behav Hum Decis Process 78 (2): 128–145.

Harrison Y, Horne JA, Rothwell A et al. (2000). Prefrontal neuropsychological effects of sleep deprivation in young adults – a model for healthy aging? Sleep 23 (8): 1067–1073.

Hashimoto K, Ono T, Honda E et al. (2006). Effects of mandibular advancement on brain activation during inspiratory loading in healthy subjects: a functional magnetic resonance imaging study. J Appl Physiol 100 (2): 579–586.

Henderson LA, Woo MA, Macey PM et al. (2003). Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. J Appl Physiol 94 (3): 1063–1074.

Ho AP, Gillin JC, Buchsbaum MS et al. (1996). Brain glucose metabolism during non-rapid eye movement sleep in major depression. A positron emission tomography study. Arch Gen Psychiatry 53 (7): 645–652.

Hobson JA (1964). [The phasic electrical activity of the cortex and thalamus during desychonized sleep in cats.]. C R Seances Soc Biol Fil 158: 2131–2135.

Hofle N, Paus T, Reutens D et al. (1997). Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. J Neurosci 17 (12): 4800–4808.

Hong SB, Tae WS, Joo EY et al. (2006). Cerebral perfusion changes during cataplexy in narcolepsy patients. Neurology 66 (11): 1747–1749.

Horne JA (1988). Sleep loss and "divergent" thinking ability. Sleep 11 (6): 528–536.

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

Hornyak M, Ahrendts JC, Spiegelhalder K et al. (2007). Voxel-based morphometry in unmedicated patients with restless legs syndrome. Sleep Med 9 (1): 22–26.

Howard RJ, Ellis C, Bullmore ET et al. (1996). Functional echoplanar brain imaging correlates of amphetamine administration to normal subjects and subjects with the narcoleptic syndrome. Magn Reson Imaging 14 (9): 1013–1016.

Hublin C, Launes J, Nikkinen P et al. (1994). Dopamine D2-receptors in human narcolepsy: a SPECT study with 123I-IBZM. Acta Neurol Scand 90 (3): 186–189.

Inoue S, Saha U, Musha T et al. (1999). Spatio-temporal distribution of neuronal activities and REM sleep. In: B Mallick, S Inoue (Eds.), Rapid Eye Movement Sleep. Narosa Publishing House, New Delhi, pp. 214–230.

Ioannides AA, Corsi-Cabrera M, Fenwick PB et al. (2004). MEG tomography of human cortex and brainstem

activity in waking and REM sleep saccades. Cereb Cortex 14 (1): 56–72.

Iranzo A, Santamaria J, Pujol J et al. (2002). Brainstem proton magnetic resonance spectroscopy in idopathic REM sleep behavior disorder. Sleep 25 (8): 867–870.

Joiner TE Jr, Steer RA, Beck AT et al. (1999). Physiological hyperarousal: construct validity of a central aspect of the tripartite model of depression and anxiety. J Abnorm Psychol 108 (2): 290–298.

Jones BE (1991). Paradoxical sleep and its chemical/structural substrates in the brain. Neuroscience 40 (3): 637–656.

Joo EY, Tae WS, Kim JH et al. (2004). Glucose hypometabolism of hypothalamus and thalamus in narcolepsy. Ann Neurol 56 (3): 437–440.

Joo EY, Tae WS, Kim JH et al. (2008). Cerebral blood flow changes in man by wake-promoting drug, modafinil: a randomized double blind study. J Sleep Res 17 (1): 82–88.

Jouvet M (1967). Neurophysiology of the states of sleep. Physiol Rev 47 (2): 117–177.

Kajimura N, Uchiyama M, Takayama Y et al. (1999). Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. J Neurosci 19 (22): 10065–10073.

Kamba M, Suto Y, Ohta Y et al. (1997). Cerebral metabolism in sleep apnea. Evaluation by magnetic resonance spectroscopy. Am J Respir Crit Care Med 156 (1): 296–298.

Kaufmann C, Schuld A, Pollmacher T et al. (2002). Reduced cortical gray matter in narcolepsy: preliminary findings with voxel-based morphometry. Neurology 58 (12): 1852–1855.

Khan N, Antonini A, Parkes D et al. (1994). Striatal dopamine D2 receptors in patients with narcolepsy measured with PET and 11C-raclopride. Neurology 44 (11): 2102–2104.

Kim SJ, Lyoo IK, Lee YS (2008). Increased GABA levels in medial prefrontal cortex of young adults with narcolepsy. Sleep 31 (3): 342–347.

Kish SJ, Mamelak M, Slimovitch C et al. (1992). Brain neurotransmitter changes in human narcolepsy. Neurology 42 (1): 229–234.

Kjaer TW, Law I, Wiltschiotz G et al. (2002). Regional cerebral blood flow during light sleep-a H(2)(15)O-PET study. J Sleep Res 11 (3): 201–207.

Kotterba S, Rasche K, Widdig W et al. (1998). Neuropsychological investigations and event-related potentials in obstructive sleep apnea syndrome before and during CPAP-therapy. J Neurol Sci 159 (1): 45–50.

Kryger MH, Roth T, Dement WC et al. (2000). Principles and Practice of Sleep Medicine. 3rd edn. W.B. Saunders, Philadelphia.

Lenzi P, Zoccoli G, Walker AM et al. (1999). Cerebral blood flow regulation in REM sleep: a model for flow-metabolism coupling. Arch Ital Biol 137 (2–3): 165–179.

Lesage S, Hening WA (2004). The restless legs syndrome and periodic limb movement disorder: a review of management. Semin Neurol 24 (3): 249–259.

Lin L, Faraco J, Li R et al. (1999). The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98 (3): 365–376.

Lodi R, Tonon C, Vignatelli L et al. (2004). In vivo evidence of neuronal loss in the hypothalamus of narcoleptic patients. Neurology 63 (8): 1513–1515.

McCarley RW, Winkelman JW, Duffy FH et al. (1983). Human cerebral potentials associated with REM sleep rapid eye movements: links to PGO waves and waking potentials. Brain Res 274 (2): 359–364.

Macey KE, Macey PM, Woo MA et al. (2006). Inspiratory loading elicits aberrant fMRI signal changes in obstructive sleep apnea. Respir Physiol Neurobiol 151 (1): 44–60.

Macey PM, Henderson LA, Macey KE et al. (2002). Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 166 (10): 1382–1387.

Macey PM, Macey KE, Henderson LA et al. (2003). Functional magnetic resonance imaging responses to expiratory loading in obstructive sleep apnea. Respir Physiol Neurobiol 138 (2–3): 275–290.

MacFarlane JG, List SJ, Moldofsky H et al. (1997). Dopamine D2 receptors quantified in vivo in human narcolepsy. Biol Psychiatry 41 (3): 305–310.

Madsen PL, Schmidt JF, Wildschiodtz G et al. (1991a). Cerebral oxygen metabolism and cerebral blood flow in man during light sleep (stage 2). Brain Res 557 (1–2): 217–220.

Madsen PL, Schmidt JF, Holm S et al. (1991b). Cerebral O_2 metabolism and cerebral blood flow in humans during deep and rapid-eye-movement sleep. J Appl Physiol 70 (6): 2597–2601.

Maquet P (2000). Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 9 (3): 207–231.

Maquet P, Phillips C (1998). Functional brain imaging of human sleep. J Sleep Res 7 (Suppl 1): 42–47.

Maquet P, Dive D, Salmon E et al. (1990). Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [^{18}F]2-fluoro-2-deoxy-D-glucose method. Brain Res 513 (1): 136–143.

Maquet P, Dive D, Salmon E et al. (1992). Cerebral glucose utilization during stage 2 sleep in man. Brain Res 571 (1): 149–153.

Maquet P, Peters J, Aerts J et al. (1996). Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383 (6596): 163–166.

Maquet P, Degueldre C, Delfiore G et al. (1997). Functional neuroanatomy of human slow wave sleep. J Neurosci 17 (8): 2807–2812.

Maquet P, Smith C, Stickgold R et al. (2003). Sleep and Brain Plasticity. Oxford University Press, Oxford.

Maquet P, Ruby P, Maudoux A et al. (2005). Human cognition during REM sleep and the activity profile within frontal and parietal cortices. A reappraisal of functional neuroimaging data. Prog Brain Res 150: 219–227.

Mateika JH, Ellythy M (2003). Chemoreflex control of ventilation is altered during wakefulness in humans with OSA. Respir Physiol Neurobiol 138 (1): 45–57.

Mayberg HS (1997). Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 9 (3): 471–481.

Mazza S, Soucy JP, Gravel P et al. (2006). Assessing whole brain perfusion changes in patients with REM sleep behavior disorder. Neurology 67 (9): 1618–1622.

Meyer JS, Sakai F, Karacan I et al. (1980). Sleep apnea, narcolepsy, and dreaming: regional cerebral hemodynamics. Ann Neurol 7 (5): 479–485.

Meyer JS, Ishikawa Y, Hata T et al. (1987). Cerebral blood flow in normal and abnormal sleep and dreaming. Brain Cogn 6 (3): 266–294.

Michaud M, Soucy JP, Chabli A et al. (2002). SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J Neurol 249 (2): 164–170.

Mignot E, Lammers GJ, Ripley B et al. (2002). The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 59 (10): 1553–1562.

Mikiten T, Niebyl P, Hendley C et al. (1961). EEG desynchronization during behavioural sleep associated with spike discharges from the thalamus of the cat. Fed Proc (20): 327.

Milak MS, Parsey RV, Keilp J (2005). Neuroanatomic correlates of psychopathologic components of major depressive disorder. Arch Gen Psychiatry 62 (4): 397–408.

Miyamoto M, Miyamoto T, Kubo J et al. (2000). Brainstem function in rapid eye movement sleep behavior disorder: the evaluation of brainstem function by proton MR spectroscopy (^{1}H-MRS). Psychiatry Clin Neurosci 54 (3): 350–351.

Montplaisir J, Lorrain D, Godbout R et al. (1991). Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanism. Eur Neurol 31 (1): 41–43.

Montplaisir J, Lapierre O, Lavigne G et al. (1994). [Movement disorders during sleep: attempt at classification.] Neurophysiol Clin 24 (2): 155–159.

Montplaisir J, Denesle R, Petit D et al. (2000). Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol 7 (Suppl 1): 27–31.

Morrell MJ, McRobbie DW, Quest RA et al. (2003). Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 4 (5): 451–454.

Mouret J, Jeannerod M, Jouvet M et al. (1963). [Electrical activity of the visual system during the paradoxical phase of sleep in the cat.] J Physiol (Paris) 55: 305–306.

Naegele B, Thouvard V, Pepin JL et al. (1995). Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 18 (1): 43–52.

Naegele B, Pepin JL, Levy P et al. (1998). Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 21 (4): 392–397.

Nofzinger EA, Mintun MA, Wiseman M et al. (1997). Forebrain activation in REM sleep: an FDG PET study. Brain Res 770 (1–2): 192–201.

Nofzinger EA, Nichols TE, Meltzer CC et al. (1999). Changes in forebrain function from waking to REM sleep in depression: preliminary analyses of [^{18}F]FDG PET studies. Psychiatry Res 91 (2): 59–78.

Nofzinger EA, Price JC, Meltzer CC et al. (2000). Towards a neurobiology of dysfunctional arousal in depression: the relationship between beta EEG power and regional cerebral glucose metabolism during NREM sleep. Psychiatry Res 98 (2): 71–91.

Nofzinger EA, Berman S, Fasiczka A et al. (2001). Effects of bupropion SR on anterior paralimbic function during waking and REM sleep in depression: preliminary findings using. Psychiatry Res 106 (2): 95–111.

Nofzinger EA, Buysse DJ, Miewald JM et al. (2002). Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain 125 (Pt 5): 1105–1115.

Nofzinger EA, Buysse DJ, Germain A et al. (2004a). Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 161 (11): 2126–2128.

Nofzinger EA, Buysse DJ, Germain A et al. (2004b). Increased activation of anterior paralimbic and executive cortex from waking to rapid eye movement sleep in depression. Arch Gen Psychiatry 61 (7): 695–702.

Nose I, Ookawa T, Tanaka J et al. (2002). Decreased blood flow of the left thalamus during somnolent episodes in a case of recurrent hypersomnia. Psychiatry Clin Neurosci 56 (3): 277–278.

O'Donoghue FJ, Briellmann RS, Rochford PD et al. (2005). Cerebral structural changes in severe obstructive sleep apnea. Am J Respir Crit Care Med 171 (10): 1185–1190.

Overeem S, Steens SC, Good CD et al. (2003). Voxel-based morphometry in hypocretin-deficient narcolepsy. Sleep 26 (1): 44–46.

Peigneux P, Laureys S, Fuchs S et al. (2001). Generation of rapid eye movements during paradoxical sleep in humans. Neuroimage 14 (3): 701–708.

Perlis ML, Smith MT, Andrews PJ et al. (2001). Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep 24 (1): 110–117.

Peyron C, Faraco J, Rogers W et al. (2000). A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 6 (9): 991–997.

Pilcher JJ, Huffcutt AI (1996). Effects of sleep deprivation on performance: a meta-analysis. Sleep 19 (4): 318–326.

Plazzi G, Corsini R, Provini F et al. (1997). REM sleep behavior disorders in multiple system atrophy. Neurology 48 (4): 1094–1097.

Portas CM, Krakow K, Allen P et al. (2000). Auditory processing across the sleep–wake cycle: simultaneous EEG and fMRI monitoring in humans. Neuron 28 (3): 991–999.

Reiss AL, Hoeft F, Tenforde AS et al. (2008). Anomalous hypothalamic responses to humor in cataplexy. PLoS ONE 3 (5): e2225.

Rinne JO, Hublin C, Partinen M et al. (1995). Positron emission tomography study of human narcolepsy: no increase in striatal dopamine D2 receptors. Neurology 45 (9): 1735–1738.

Rinne JO, Hublin C, Partinen M et al. (1996). Striatal dopamine D1 receptors in narcolepsy: a PET study with [^{11}C] NNC 756. J Sleep Res 5 (4): 262–264.

Sakai K, Sastre JP, Karacan I et al. (1979). Tegmentoreticular projections with special reference to the muscular atonia during paradoxical sleep in the cat: an HRP study. Brain Res 176 (2): 233–254.

Sakurai T (2005). Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy homeostasis. Sleep Med Rev 9 (4): 231–241.

Salzarulo P, Lairy GC, Bancaud J et al. (1975). Direct depth recording of the striate cortex during REM sleep in man: are there PGO potentials? Electroencephalogr Clin Neurophysiol 38 (2): 199–202.

Saper CB, Chou TC, Scammell TE et al. (2001). The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 24 (12): 726–731.

Sastre JP, Buda C, Lin JS et al. (2000). Differential c-fos expression in the rhinencephalon and striatum after enhanced sleep–wake states in the cat. Eur J Neurosci 12 (4): 1397–1410.

Schabus M, Dang-Vu TT, Albouy G et al. (2007). Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A 104 (32): 13164–13169.

Schenck CH, Bundlie SR, Ettinger MG et al. (1986). Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 9 (2): 293–308.

Schenck CH, Bundlie SR, Mahowald MW et al. (1996). Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 46 (2): 388–393.

Schroder CM, O'Hara R (2005). Depression and obstructive sleep apnea (OSA). Ann Gen Psychiatry 4: 13.

Schwartz S, Ponz A, Poryazova R et al. (2008). Abnormal activity in hypothalamus and amygdala during humour processing in human narcolepsy with cataplexy. Brain 131: 514–522.

Shirakawa S, Takeuchi N, Uchimura N et al. (2002). Study of image findings in rapid eye movement sleep behavioural disorder. Psychiatry Clin Neurosci 56 (3): 291–292.

Smith GS, Reynolds CF 3rd, Pollock B et al. (1999). Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. Am J Psychiatry 156 (5): 683–689.

Smith MT, Perlis ML, Chengazi VU et al. (2002). Neuroimaging of NREM sleep in primary insomnia: a Tc-99-HMPAO single photon emission computed tomography study. Sleep 25 (3): 325–335.

Smith MT, Perlis ML, Chengazi VU et al. (2005). NREM sleep cerebral blood flow before and after behavior therapy for chronic primary insomnia: preliminary single photon emission computed tomography (SPECT) data. Sleep Med 6 (1): 93–94.

Spiegel K, Tasali E, Penev P et al. (2004). Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 141 (11): 846–850.

Staedt J, Stoppe G, Kogler A et al. (1993). Dopamine D2 receptor alteration in patients with periodic movements in sleep (nocturnal myoclonus). J Neural Transm Gen Sect 93 (1): 71–74.

Staedt J, Stoppe G, Kogler A et al. (1995a). Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alteration. Eur Arch Psychiatry Clin Neurosci 245 (1): 8–10.

Staedt J, Stoppe G, Kogler A et al. (1995b). Single photon emission tomography (SPET) imaging of dopamine D2 receptors in the course of dopamine replacement therapy in patients with nocturnal myoclonus syndrome (NMS). J Neural Transm Gen Sect 99 (1–3): 187–193.

Staedt J, Stoppe G, Kogler A et al. (1996). $[^{123}I]$IBZM SPET analysis of dopamine D2 receptor occupancy in narcoleptic patients in the course of treatment. Biol Psychiatry 39 (2): 107–111.

Stepanski E, Zorick F, Roehrs T et al. (1988). Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. Sleep 11 (1): 54–60.

Steriade M, Amzica F (1998). Coalescence of sleep rhythms and their chronology in corticothalamic networks. Sleep Res Online 1 (1): 1–10.

Steriade M, McCarley RW (1990). Brainstem Control of Wakefulness and Sleep. Plenum Press, New York.

Steriade M, Timofeev I (2003). Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 37 (4): 563–576.

Steriade M, Nunez A, Amzica F et al. (1993). Intracellular analysis of relations between the slow (< 1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci 13 (8): 3266–3283.

Stickgold R, Walker MP (2007). Sleep-dependent memory consolidation and reconsolidation. Sleep Med 8 (4): 331–343.

Sudo Y, Suhara T, Honda Y et al. (1998). Muscarinic cholinergic receptors in human narcolepsy: a PET study. Neurology 51 (5): 1297–1302.

Szuba MP, Baxter LR Jr, Fairbanks LA et al. (1991). Effects of partial sleep deprivation on the diurnal variation of mood and motor activity in major depression. Biol Psychiatry 30 (8): 817–829.

Tan EK, Ondo W (2000). Restless legs syndrome: clinical features and treatment. Am J Med Sci 319 (6): 397–403.

Tasali E, Van Cauter E (2002). Sleep-disordered breathing and the current epidemic of obesity: consequence or contributing factor? Am J Respir Crit Care Med 165 (5): 562–563.

Thannickal TC, Siegel JM, Nienhuis R et al. (2003). Pattern of hypocretin (orexin) soma and axon loss, and gliosis, in human narcolepsy. Brain Pathol 13 (3): 340–351.

Thase ME (1998). Depression, sleep, and antidepressants. J Clin Psychiatry 59 (Suppl 4): 55–65.

Thase ME, Buysse DJ, Frank E et al. (1997). Which depressed patients will respond to interpersonal psychotherapy? The role of abnormal EEG sleep profiles. Am J Psychiatry 154 (4): 502–509.

Tonon C, Vetrugno R, Lodi R et al. (2007). Proton magnetic resonance spectroscopy study of brain metabolism in obstructive sleep apnoea syndrome before and after continuous positive airway pressure treatment. Sleep 30 (3): 305–311.

Trenkwalder C (1998). Sleep dysfunction in Parkinson's disease. Clin Neurosci 5 (2): 107–114.

Tribl GG, Asenbaum S, Happe S et al. (2004). Normal striatal D2 receptor binding in idiopathic restless legs syndrome with periodic leg movements in sleep. Nucl Med Commun 25 (1): 55–60.

Unrath A, Juengling FD, Schork M (2007). Cortical grey matter alterations in idiopathic restless legs syndrome: an optimized voxel-based morphometry study. Mov Disord 22 (12): 1751–1756.

Unrath A, Muller HP, Ludolph AC et al. (2008). Cerebral white matter alterations in idiopathic restless legs syndrome, as measured by diffusion tensor imaging. Mov Disord 23 (9): 1250–1255.

Watanabe S, Sakai K, Ono Y et al. (1987). Alternating periodic leg movement induced by spinal anesthesia in an elderly male. Anesth Analg 66 (10): 1031–1032.

Wehrle R, Czisch M, Kaufmann C et al. (2005). Rapid eye movement-related brain activation in human sleep: a functional magnetic resonance imaging study. Neuroreport 16 (8): 853–857.

Wetter TC, Pollmacher T (1997). Restless legs and periodic leg movements in sleep syndromes. J Neurol 244 (4 Suppl 1): S37–S45.

Wirz-Justice A, Van den Hoofdakker RH (1999). Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry 46 (4): 445–453.

Wu JC, Gillin JC, Buchsbaum MS et al. (1992). Effect of sleep deprivation on brain metabolism of depressed patients. Am J Psychiatry 149 (4): 538–543.

Wu J, Buchsbaum MS, Gillin JC et al. (1999). Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry 156 (8): 1149–1158.

Wu JC, Gillin JC, Buchsbaum MS et al. (2008). Sleep deprivation PET correlations of Hamilton symptom improvement ratings with changes in relative glucose metabolism in patients with depression. J Affect Disord 107 (1–3): 181–186.

Yeon Joo E, Hong SB, Tae WS et al. (2005). Cerebral perfusion abnormality in narcolepsy with cataplexy. Neuroimage 28: 410–416.

Young T, Blustein J, Finn L et al. (1997). Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep 20 (8): 608–613.

Young T, Peppard PE, Gottlieb DJ et al. (2002). Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 165 (9): 1217–1239.