Chapter 6

Functional neuroimaging in sleep, sleep deprivation, and sleep disorders

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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; Buysaki, 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, thalamus, 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

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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 thalamocortical 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 thalamocortico-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

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**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 (µV²) 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 (2003). 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 (Home, 1988, 1995; Pilcher and Huffman, 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, prefrontal, posterior cingulate cortex, and parahippocampal gyrus (Dang-Vu et al., 2008). Besides 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; Noefinger et al., 1997), hippocampal formation (Braun et al., 1997; Noefinger et al., 1997), and anterior cingulate cortex (Maquet et al., 1996; Braun et al., 1997; Noefinger et al., 1997)). Posterior cortices in temporo-occipital areas were also found to be activated (Braun et al., 1997; Wohrle 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; Noefinger et al., 1997; Wohrle 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; Noefinger 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 the 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 18F-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 entorhinal 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, cingu-
luate gyrus) (Hobson, 1964). Using PET, regional CBF in
the lateral genulate bodies and the occipital cortex was
shown to be more tightly coupled to spontaneous
eye movements during REM sleep than during wake-
fulness (Polgeaux 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 (Wohle
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 sig-
nal were localized in the brainstem, thalamus, hippo-
campus 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 sug-
gest that the processing of external stimuli persists
during NREM sleep. A pioneering fMRI study found
that during NREM sleep, as during wakefulness, sev-
eral areas continue to be activated by external auditory
stimulation: the thalamic nuclei, the auditory cortices,
and the caudate nucleus (Portas et al., 2000). More-
ever, the left amygdala and the left prefrontal 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 com-
pared 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 dis-
order (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., anx-
xiety, depression, schizophrenia). From the latter condi-
tions, we will only consider the sleep disorders
secondary to depression.

Single case reports of brain functional imaging like
in recurrent hypersonnia (Nosic 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 ade-
quate 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 cor-
tical hyperarousal in insomnia (Perlis et al., 2001).
However, it should be noticed that hyperarousal in pri-
mary 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 insomniia while
others report a decrease in cortical functions. In the
latter, decreased metabolism might originate from the
time window coincidence of the cortical hyperarousal
period with neuroimaging acquisition, and therefore
does not discard the hyperarousal hypothesis of pri-
mary 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 (99mTc-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 medially, 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 18F-fluorodeoxyglucose (18FDG) PET in 7 patients with idiopathic insomnia and 20 healthy age- and gender-matched subjects during waking and NREM sleep (Nozinger 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 (Nozinger 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 (Bena, 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

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**Fig. 6.3.** Regional cerebral glucose metabolism (CMRglu) in patients with insomnia assessed during both waking and nonrapid eye movement sleep states by using 18F-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 Nozinger 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 18F-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 18F-FDG PET study (Nolzinger 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) (Nolzinger 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 medial 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 (Nozinger 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 (Nozinger 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 (Nozinger et al., 2004b) and in the tectal area, inferior temporal cortex, amygdala, and subicular complex (Nozinger 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 gyrus (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 (Nozinger 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 medial 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 hypnotagogic hallucinations (Meyer et al., 1980, 1987).

In another study, 6 narcoleptic patients underwent \textsuperscript{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, thalamus, 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, thalamus, 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 gyr, an area involved in inhibition (Aron et al., 2004). In addition a reduction in hypothalamic activity was shown in 1 subject experiencing a cataleptic 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 cataplexy and sleep attacks in 7 patients with narcolepsy (Eisele et al., 1992a). 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., 1995) studies. This discrepancy might be related to the drug treatment of narcoleptic patients. Indeed, considerable increase in the uptake of \textsuperscript{129}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 (Stuedt 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 amphetamine 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 thalamus, dorsolateral prefrontal, orbitofrontal, superior frontal, and middle frontal gyri, insular gyri, cingulate gyrus, inferior temporal gyrus, and parahippocampal gyrus) (Ugo 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 (glutamnergic) 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 (1H-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
FUNCTIONAL NEUROIMAGING IN SLEEP, SLEEP DEPRIVATION, AND SLEEP DISORDERS

patients (Lodi et al., 2004). In both studies, an analysis of spectral peak area ratios revealed a decrease in the NAA/creatinine-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 1H-MRS study in 17 narcoleptic 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 18FDG PET study that was used to measure relative differences between CMRGlut of 24 narcoleptic patients and 24 normal controls during wakefulness (Joo et al., 2004) (Figure 6.4). Narcoleptic patients had reduced CMRGlut in bilateral prefrontal, bilateral posterior hypothalamus, and mediodorsal thalamic nuclei (Joo et al., 2004). This study prevails over a SPECT study that was subsequently conducted (Yeon 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 hypoxic episodes (Caples et al., 2005). Furthermore, 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 (Atchamatis 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 (CMRGlut) in the hypothalamus and thalamus in narcoleptic patients during wakefulness.

Bilateral posterior hypothalamus 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 (Naegle et al., 1995; Feuerstein et al., 1997), deficits in working memory (Greenberg et al., 1987; Naegle 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; Naegle 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 (Cale 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 1H-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 1H-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 Hallower 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 $^9$mTc-HMPAO SPECT study in 14 adult OSAS patients (Flicker 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 (Tonom 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, cerebellum, frontal cortex, and thalami.

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 lenticuliform 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
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 (Tasli 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 Pollracher, 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 (Akpınar, 1982), whereas dopaminergic drugs have been shown to relieve PLMS (Brodceur 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 \( ^{2} \text{H}-\text{IBZM} \) 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 (Tribel 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 substantia 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 \( R_g^* \), Allen et al. (2001) assessed regional brain iron concentrations in 10 subjects (5 with RLS, 5 controls). \( R_g^* \) 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 \( R_g^* \) 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 parkinsonism 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., 1970).

A study combining MRI and \( ^{2} \text{H}-\text{IMP} \) 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 \( ^{1} \text{H-MRS} \) 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 \( ^{1} \text{H-MRS} \) 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/creatinine 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 \( ^{1} \text{H-MRS} \) detectable metabolic disturbances in idiopathic RBD. Despite these equivocal results, \( ^{1} \text{H-MRS} \) 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 \((\text{N})-(3\text{-iodopropene-2-yl})\text{-2beta-carboxymethoxy-3beta-(4-chlorophenyl) tropane labeled with iodine-123 (IPT)}\), 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 \((n = 14)\) (Eisenhre et al., 2000, 2003b). These results suggest that the number of presynaptic dopamine transporters is decreased in both Parkinson and RBD patients. Other studies proved the density of striatal dopaminergic terminals using PET and \( ^{1} \text{H-dihydrotetrabenazine (H-DTBZ)} \), 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 \(^{125}I\)-labeled benzovesamol (\(^{125}I\)-IBVM) binding was reduced in the thalamus in this MSA population. \(^{125}I\)-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.

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FUNCTIONAL NEUROIMAGING IN SLEEP, SLEEP DEPRIVATION, AND SLEEP DISORDERS


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