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Neuroimaging in sleep medicine

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Abstract

The development of neuroimaging techniques has made possible the characterization of cerebral function throughout the sleep-wake cycle in normal human subjects. Indeed, human brain activity during sleep is segregated within specific cortical and subcortical areas in relation to the sleep stage, sleep physiological events and previous waking activity. This approach has allowed sleep physiological theories developed from animal data to be confirmed, but has also introduced original concepts about the neurobiological mechanisms of sleep, dreams and memory in humans. In contrast, at present, few neuroimaging studies have been dedicated to human sleep disorders. The available work has brought interesting data that describe some aspects of the pathophysiology and neural consequences of disorders such as insomnia, sleep apnea and narcolepsy. However, the interpretation of many of these results is restricted by limited sample size and spatial/temporal resolution of the employed technique. The use of neuroimaging in sleep medicine is actually restrained by concerns resulting from the technical experimental settings and the characteristics of the diseases. Nevertheless, we predict that future studies, conducted with state of the art techniques on larger numbers of patients, will be able to address these issues and contribute significantly to the understanding of the neural basis of sleep pathologies. This may finally offer the opportunity to use neuroimaging, in addition to the clinical and electrophysiological assessments, as a helpful tool in the diagnosis, classification, treatment and monitoring of sleep disorders in humans.

Keywords: Sleep disorders; PET; SPECT; fMRI; REM; non-REM

1. Introduction

Public authorities and the general population are beginning to realize the importance of sleep medicine, with respect to the high prevalence of sleep disorders and their great impact on quality of life, morbidity/mortality, public health and productivity. The increasing development of sleep laboratories and polysomnography has allowed clinicians to diagnose and treat efficiently a growing number of patients with sleep complaints. However, many questions about the pathophysiology of sleep disorders remain unanswered using clinical, neurophysiological and biological assessment. Optimal management of sleep disorders requires a comprehensive understanding of their pathological mechanisms, which first requires a good knowledge of sleep physiology.

During the past few decades, the development of neuroimaging has provided an important tool of non-invasive investigation allowing for the detection of subtle anatomical changes as well as variations in cerebral

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blood flow, metabolism and neurotransmission. In the field of sleep research, neuroimaging has provided interesting insight about human sleep physiology by presenting functional brain maps in different sleep stages [1–3] that are in part corroborated by previous animal experimental data, and by giving support to a role of sleep in learning and memory [4,5]. Although considerable progress has been made, our understanding of basic sleep physiology still remains fragmentary. As for the use of neuroimaging in sleep pathology, it is still in its infancy. There have been important contributions to the understanding of some sleep disorders, but many studies have been conducted using single cases or few subjects.

In this article, we will review critically the available neuroimaging studies conducted in patients with sleep disorders, with an emphasis on the limitations of these studies as well as on potential future directions. We will begin with a review of neuroimaging studies conducted in normal human subjects, because these data constitute a baseline for the interpretation of findings in sleep disorders.

2. Neuroimaging in normal human sleep

2.1. Functional neuroanatomy of sleep stages

During the last decade, positron emission tomography (PET), using [^{15}O]-labeled water ($H_2{}^{15}O$) or [^{18}F] fluorodeoxyglucose (^{18}FDG), and functional magnetic resonance imaging (fMRI) were used to describe the functional neuroanatomy of normal human sleep. These studies show that global and regional patterns of brain activity during sleep are remarkably different from those obtained during wakefulness. Neuroimaging studies also highlight major functional differences between rapid eye movement (REM) sleep and non-REM sleep.

2.1.1. Non-REM sleep

Non-REM sleep, when compared to wakefulness or REM sleep [1,3,6–8], is characterized by a global decrease in cerebral blood flow, and a decrease in regional cerebral blood flow (rCBF) in the dorsal pons, mesencephalon, thalami, basal ganglia, basal forebrain and anterior hypothalamus, prefrontal cortex, anterior cingulate cortex and precuneus (Fig. 1, right panel).

Deactivation in the brainstem and thalamus is in agreement with non-REM sleep generation mechanisms in mammals, in which a decreased firing rate in brainstem structures causes a hyperpolarization of thalamic neurons and a cascade of events inducing the formation of non-REM sleep rhythms (e.g., spindles, K-complexes, delta and slow oscillations). A meta-analysis of PET data assessing correlations between rCBF and delta activity during non-REM sleep showed a similar brain mapping except for the thalamus, in which rCBF was not correlated with delta activity, even at a low statistical threshold [9] (Fig. 1, left panel). This result suggests the potential importance of an extra-thalamic delta rhythm among non-REM sleep synchronous oscillations.

Neuroimaging data also show that the pattern of deactivation is not homogeneously distributed throughout the cortex. As compared to wakefulness, the least active areas in non-REM sleep were observed in various associative cortices of the frontal (in particular in the dorsolateral prefrontal [DLPF] and orbital prefrontal cortex), parietal – and less consistently in the temporal and insular – lobes [1,3,7,8]. An inverse relationship between delta activity and rCBF is found in ventromedial prefrontal regions [VMPF] (medial frontal, anterior cingulate and orbito-frontal) during non-REM sleep [9]. In contrast, the primary cortices were the least deactivated cortical areas [3]. The reasons for this heterogeneous cortical distribution remain unclear. One

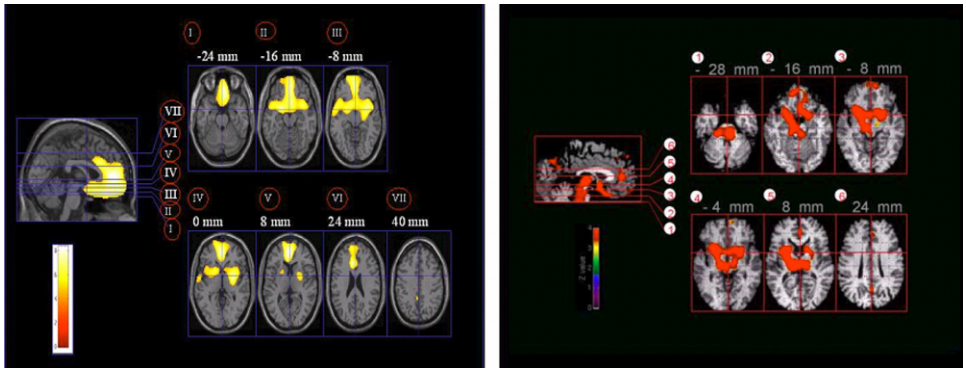

Fig. 1. Functional neuroanatomy of normal human non-REM sleep, assessed by $H_2{}^{15}O$ PET. (Left panel) Brain areas in which regional cerebral blood flow (rCBF) decreases as a function of delta power during non-REM sleep (stages 2–4). Image sections are displayed on different levels of the z axis as indicated on the top of each picture [216]. The color scale indicates the range of Z values for the activated voxels. Displayed voxels are significant at $P < 0.05$ after correction for multiple comparisons. (Right panel) Brain areas in which rCBF decreases during non-REM sleep as compared to wakefulness and REM sleep [1]. Note the similarity of the regional blood flow distribution between left and right panels. Copyright 1997 by the Society for Neuroscience. Reprinted from Neuroimage; vol. 28(1); Dang-Vu TT, Desseilles M, Laureys S, Degueldre C, Perrin F, Philips C, Maquet P and Peigneux P. "Cerebral correlates of delta waves during non-REM sleep revisited"; pp. 14–21; Copyright 2005, with permission from Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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 [10], these cortices might be more profoundly influenced by non-REM sleep rhythms than primary cortices [6].

Another area where the rCBF is significantly decreased is the precuneus [1,3,8]. Interpretation of this finding remains uncertain. As the precuneus is a region particularly active during wakefulness, its decreasing activity during non-REM sleep may reflect more the waning of waking-dependent processes rather than sleep-promoting mechanisms [6]. Intriguingly, it is interesting to note that the precuneus is also deactivated during states of decreased consciousness like pharmacological sedation [11], hypnotic [12] and vegetative states [13].

Deactivations during non-REM sleep were also located in the basal forebrain and the basal ganglia [1,3,7]. The basal forebrain and anterior hypothalamus (BF/AH) form a functionally and structurally heterogeneous structure [14], in which a majority of neurons are involved in cortical activation during wakefulness and REM sleep [15]. The deactivation of BF/AH would, therefore, be compatible with a lower activity of these arousal-promoting neurons during non-REM sleep. The role of the basal ganglia, and especially the striatum, in sleep regulation is still poorly understood. On one hand, as the frontal cortex and the thalamus are both among the most deactivated brain areas during non-REM sleep and also major afferents to basal ganglia [16–18], it has been proposed that the decreasing activity in these regions could entrain the basal ganglia neuronal population in highly synchronized oscillations during non-REM sleep [6] with long phases of hyperpolarization alternating with bursts of discharges [19]. On the other hand, afferents arising from the striatum may entrain the disinhibition of the pedunculopontine tegmental nucleus (PPT) and result in cortical activation, thus promoting wakefulness [20]. Therefore, the decreasing activity in the striatum during non-REM sleep could also be related to a lower propensity to arousal. Finally, links between delta activity and the gene encoding the retinoic acid receptor beta (*Rarb*) were recently evidenced in mice [21]. Interestingly, other studies suggest that *Rarb* plays a major role in the mesolimbic dopaminergic pathway [22,23], which projects from the midbrain ventral tegmental area to the ventral striatum.

2.1.2. REM sleep

In contrast to non-REM sleep, REM sleep is characterized by sustained neuronal activity [24,25], high cerebral energy requirements [26] and cerebral blood flow [27,28]. When compared to wakefulness and/or non-REM sleep, regional activations during REM sleep were found in the pontine tegmentum, thalamus, amygdala, hippocampus, anterior cingulate cortex, temporo-occipital areas, basal forebrain, cerebellum and caudate nucleus; conversely, regional deactivations were located in the DLPF, posterior cingulate gyrus, the precuneus and inferior parietal cortex [2–4,29,30] (Fig. 2).

Activation of the pontine tegmentum, thalamic nuclei and basal forebrain is in agreement with REM sleep generation mechanisms in animals [31–33]. REM sleep is generated by cholinergic processes arising from brainstem structures, located in the PPT and laterodorsal tegmentum (LDT) [31,34–40], that mediate widespread cortical activation by way of a dorsal pathway

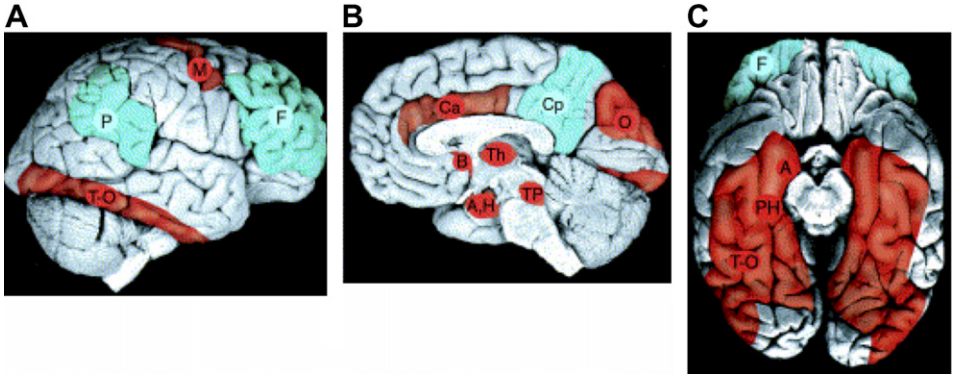

Fig. 2. Schematic representation of the functional neuroanatomy of normal human REM sleep, integrating data from PET and fMRI [2–4,29]. Regions colored in red are those in which there is a relative increase in neural activity associated with REM sleep; those in blue correspond to relative decreases in neural activity associated with REM sleep. (A) lateral view; (B) medial view; (C) ventral view. A, amygdala; B, basal forebrain; Ca, anterior cingulate gyrus; Cp, posterior cingulate gyrus and precuneus; F, prefrontal cortex (middle, inferior and orbito-frontal cortices); H, hypothalamus; M, motor cortex; P, parietal cortex (inferior parietal lobule); PH, parahippocampical gyrus; O, occipital-lateral cortex; Th, thalamus; T-O, temporo-occipital extrastriate cortex; TP, pontine tegmentum. Reprinted from Trends in Cognitive Sciences; vol. 6(1); Schwartz S, Maquet P; "Sleep imaging and the neuro-psychological assessment of dreams"; pp. 23–30; Copyright 2002, with permission from Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

innervating the thalamus, and a ventral pathway innervating the basal forebrain [41–44].

Activation of limbic and paralimbic structures, including amygdaloid complexes, hippocampal formation and anterior cingulate cortex, is also a highly reproducible finding [2,3,29]. 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 in animals, were increased in cats by electrical stimulation of the central nucleus of amygdaloid complexes [45], while carbachol (cholinergic agonist) injections in the same nucleus enhanced both REM sleep and PGO activity [46]. Besides, a $H_2{}^{15}O$ PET study found correlations during REM sleep, but not during wakefulness, between spontaneous eye movements and rCBF in the occipital cortex and the lateral geniculate bodies of the thalamus, supporting the hypothesis that PGO-like activities also contribute to shape the functional brain mapping of REM sleep in humans [47]. This finding has been recently confirmed by an fMRI study [48]. The amygdala seems to modulate other key features of REM sleep. For instance, the large variability in heart rate during REM sleep could be explained by a prominent influence of the amygdaloid complexes [49]. Both amygdala and hippocampal formation are also critical for memory systems [50] and may, thus, participate in the processing of memory traces during REM sleep, as reviewed elsewhere [51–55].

Activated temporo-occipital areas included inferior temporal cortex and fusiform gyrus, which are extrastriate cortices belonging to the ventral visual stream [3]. Additionally, the functional interactions between posterior cortical areas appeared to be different during REM sleep when compared to wakefulness [56]: extrastriate cortex activation was significantly correlated with primary visual cortex (striate cortex) deactivation during REM sleep, while their activities are usually positively correlated during wakefulness. Along with the concomitant paralimbic/limbic activation and associative areas of deactivation (see below), this pattern of functional connectivity is consistent with the model in which REM sleep allows internal information processing (between extrastriate areas and their paralimbic projections) in a closed system, dissociated from input (via striate cortex) or output (via frontal cortex) to the external world. Activations during REM sleep were also observed, less reproducibly, in the cerebellum and caudate nucleus [3]. However, the role of these structures in REM sleep physiology remains highly speculative. Activation of the cerebellar vermis might reflect input from the brainstem vestibular nuclei [3], and the caudate nucleus might play a role in the ascending thalamocortical activation [3,29].

PET studies found regional deactivations during REM sleep in the DLPF (inferior and middle frontal gyrus), precuneus, posterior cingulate cortex and part of the parietal cortex (temporo-parietal region, inferior parietal lobule) [2,3,30]. In contrast, the activity in the superior parietal lobe and in the superior and medial prefrontal cortex was similar to that in waking levels [30]. The reasons for these deactivations are still unclear. Interestingly, animal data showed that the cortical areas less active during REM sleep (inferior parietal, DLPF) received only few inputs from the amygdala, while areas more active during REM sleep (anterior cingulate, right parietal operculum) received rich amygdalar inputs [57], suggesting that the amygdala may modulate cortical activity during REM sleep. This hypothesis is also supported by the demonstration that functional interactions between the amygdala and the occipito-temporal cortices were different in the context of REM sleep than in non-REM sleep or wakefulness [58]. The amygdalo-cortical network during REM sleep might contribute in particular to the selective processing of emotionally relevant memories [2], but this speculation needs further experimental investigation.

2.2. Neuroimaging and dreams

Most studies about human dream organization have focused on REM sleep, because dreams during this sleep stage are more frequent, longer, more vivid and contain more bizarre features [59]. The ''canonical'' maps of regional cerebral activity during REM sleep, as described above, might then also be interpreted in light of some typical dreaming features [60–62]. Following are several examples.

First, perceptual features are essential characteristics of dreams: visual components are literally always present, auditory components are present in 40–60% of dreams, movement and tactile sensations in 15–30%, and finally smell and taste in less than 1% [63]. The activation of posterior (occipito-temporal) cortices may, therefore, account for the perceptual aspects of dreams, consistently dominated by visual and auditory elements [3]. Indeed, a cessation of visual dream imagery was reported in some patients with occipito-temporal lesions [64].

Dream content is also characterized by the prominence of emotions, and especially negative emotions such as fear and anxiety [63,65]. The amygdala is known to play a central role in the modulation of responses to threatening stimuli or stressful situations during wakefulness [66]. The high limbic activity during REM sleep, and especially amygdalar activation [2], could, thus, be related to the high emotional load of dream contents. Moreover, some evidence suggests that the organization of emotional experience during dreams may not imply one structure alone but a network of functionally connected areas including the amygdala and extrastriate cortices [58]. Accordingly, a recent fMRI study

conducted during wakefulness emphasized the positive relationship between emotional intensity of visual stimuli and both amygdalar and infero-temporal cortex activity; a strong linear correlation was additionally found between activity in these two structures across picture contents [67].

The prefrontal regions deactivated during REM sleep overlap with the regions supporting the contextual and episodic control of stimulus–response associations, which correspond, respectively, to the selection of these associations according to contextual signals, and previous events or internal goals [30,68]. These control levels would, therefore, be less efficient during REM sleep, potentially leading to some bizarre features of dream reports. For instance, it would explain the lack of "orientational stability", that is, the fact that the dreamer is generally unable to integrate information of a whole episode, in that the "persons, times and places are fused, incongruous and discontinuous" [61]. It may also account for the decrease in volitional control and the failure to organize one's mental representation toward a well identified internal goal and to "control the flow of dream events" [59].

These less active prefrontal areas also include frontal regions that are reported to have a role in episodic memory, that is, the ability to encode and recollect personally experienced events set in a particular spatio-temporal context [69]. Prefrontal areas would participate in the monitoring of episodic memory retrieval, especially by checking the accuracy and completeness of the processed information [30]. The deactivation of these areas during REM sleep might explain that, while 65% of dream reports contain residues of recent waking activity, only 1.4% of them are considered as representing the replay of full memory episodes [70]. Therefore, episodic elements might be reactivated in a fragmented fashion during dreams in relation with the hypoactivity of the prefrontal cortex, which would prevent the various details of past events to be integrated into an identifiable life episode [71] (for review, see [72]).

These assumptions are of great interest for the understanding of dream physiology but remain largely speculative and partial, notably because combined dream and functional imaging data are still very sparse. The future contribution of neuroimaging techniques to dream research would probably need the systematic quantification of dream content in terms of explanatory variables to model neuroimaging data [60,62]. This implies the use of scales to parameterize the dream narrative in order to assess its different perceptual, emotional, or bizarre elements and to provide genuine functional maps of the dreaming brain. As little is known about the physiology of non-REM sleep dreaming, future neuroimaging studies should also attempt to link dreaming experiences during this sleep stage with patterns of regional cerebral activity.

2.3. Sleep and memory

Besides these "canonical" maps of normal human sleep, other studies focused on more dynamic interactions during REM or non-REM sleep, such as reactivations of areas involved in learning prior to sleep. On the one hand, several structures, including premotor cortical areas (Fig. 2), were reactivated during REM sleep in subjects previously trained on a procedural motor learning task compared to non-trained subjects [4]. Such reactivations did not occur if the subjects were submitted to a random version of the same task [73]. By showing this REM sleep-related reactivation of areas activated during task learning, the study suggests a reprocessing during REM sleep of procedural memory traces acquired during previous wakefulness. On the other hand, hippocampal areas that were activated during a spatial learning task were reactivated during subsequent non-REM sleep [5], therefore suggesting a reprocessing during non-REM sleep of recent spatial memory traces acquired during previous wakefulness. Moreover, this study originally demonstrated a significant correlation between rCBF increases in hippocampal areas during non-REM sleep and the overnight gain in behavioral performance, indicating that this offline reprocessing is somehow related to plastic changes underlying a subsequent improvement in performance.

These above studies contribute to the large body of evidence supporting a role of sleep in learning and memory [51–55]. In particular, they are in line with behavioral data suggesting that REM sleep and non-REM sleep differentially modulate the consolidation of procedural and spatial/episodic memories, respectively, in the model called the dual process hypothesis [74,75]. However, these data do not allow us to discard the sequential hypothesis in which the ordered succession of non-REM sleep and REM sleep would be necessary for the consolidation of memory traces, whatever the memory system [76–78]. These models should not be viewed as mutually exclusive and still await further investigation.

3. Neuroimaging in sleep disorders

As reported in the previous sections, we have now a significant body of findings about the physiology of normal human sleep from functional imaging methods. Indeed, most neuroimaging studies of sleep have been conducted in healthy populations, which are more easily recruited and managed in these experimental conditions. There is a great diversity of environmental situations and disorders in which sleep is disturbed. In this section, we will review some neuroimaging studies focused on several specific sleep disorders, including primary sleep disorders as well as sleep disorders associated with psychiatric or neurological conditions. As stated before, the contribution of functional imaging to the study of sleep

disorders is still very fragmentary. A special emphasis will be put on some aspects that should deserve further investigation.

3.1. Sleep deprivation

Lack of sleep is a common consequence of many sleep disorders, such as sleep apnea syndrome, insomnia and restless legs/periodic limb movements disorder. It is also occasionally experienced in many life circumstances, such as traumatic events or periods of high anxiety, and chronically encountered by people living in noisy environments or working under irregular schedules (e.g., military personnel, pilots, medical workers, etc.). Related public health concerns are very important since sleep deprivation (SD) is one major cause of serious accidents in real-world situations, for instance accounting for a considerable proportion of vehicle accidents [79,80]. At the level of brain function, some consequences of SD may be shared by these various etiological conditions [81]. Therefore, several neuroimaging studies have assessed the impacts of experimentally produced SD on the waking brain function of normal subjects, in order to characterize the brain activity alterations underlying the resulting neurobehavioral impairments (i.e., decreased alertness and cognitive performance on specific tasks).

An early study used the ^{18}FDG PET method to assess the effects of 32 h of SD on the waking cerebral metabolism. There was no significant change in global cerebral metabolic rate for glucose (CMRGlu), but regional relative decreases in the temporal lobes and increases in the visual cortex were found, in parallel with a reduced performance to a visual vigilance test [82]. Using the same neuroimaging technique but with a different duration of SD (24, 48 and 72 h), Thomas and colleagues found a decline in the global CMRGlu and a relative decrease in the prefrontal cortex and thalamus that was larger after 48 and 72 h of SD than after 24 h [83,84]. These results were interpreted to reflect the homeostatic need for recuperation during sleep of these regions mediating attention and higher-order cognitive processes. Indeed, the regional decreases were positively correlated with the impairments in cognitive performance on an SD-sensitive serial addition/subtraction test, which combines arithmetic processing and working memory. Relative regional increases were noticed in visual and motor areas (e.g, lateral superior occipital cortices, lingual and fusiform gyri, anterior cerebellum, primary and supplementary motor cortices) but only after 48 and 72 h of SD. This recruitment of additional brain regions during prolonged SD was interpreted as reflecting the subjects' efforts to maintain alertness and cognitive performance [84].

Other studies used fMRI to assess the effects of SD on brain activity. Drummond and colleagues scanned normal subjects during different cognitive tasks after a normal night of sleep and following 35 h of SD. In a first report, they used a task similar to the one used by Thomas and colleagues (serial subtraction). Bilateral activations in the prefrontal, parietal and premotor cortices were found during task practice after a normal night of sleep, whereas activity in these regions declined markedly after SD, mainly in the prefrontal cortex [85], which is in agreement with the hypothesis of prefrontal cortex vulnerability to SD [86]. However, a very different pattern emerges when using other types of tasks. Indeed, during a verbal learning paradigm, prefrontal and parietal cortices were found *more* activated after SD than after normal sleep, although SD subjects performed worse and were more sleepy than controls [87]. Additionally, in the SD group, activity within the prefrontal cortex was positively correlated with subjective sleepiness while activity within the parietal lobes was associated with a better performance on the verbal learning task. Drummond and colleagues have proposed that these patterns may reflect compensatory changes in brain activation during verbal learning after SD: increased prefrontal cortex activity may represent compensation for the enhanced homeostatic drive for sleep, and increased parietal lobe activity could underlie the behavioral adaptations to SD in order to preserve an optimal performance. Similar activations and correlations were found after SD, during a divided attention paradigm that combines their previously reported verbal learning and arithmetic tasks [88]. Mu and colleagues found reduced activations in several regions (left DLPF, right ventrolateral prefrontal cortex [VLPF], supplementary motor area [SMA], Broca's area, bilateral posterior parietal cortices [PPC]) but no significant increased activations during practice of the Sternberg working memory task (SWMT) after 30 h of SD compared to normal sleep [89]. Altogether, these results suggest that brain responses to SD may be at least partially task-specific [85,87,89].

Not only the type of task but also its level of difficulty may modulate the cerebral responses to SD [90]. Accordingly, Drummond and colleagues found that increasing task demands in a logical reasoning paradigm induced stronger responses in several cortical areas (e.g., bilateral inferior parietal lobes, left inferior frontal gyrus and left DLPF) after SD than after normal sleep, and also elicited new responses in other regions (e.g., left anterior cingulate, bilateral temporal cortex) following SD but not after normal sleep [90]. It has also been shown that increasing the complexity of a verbal working memory task elicits a greater activation of the left DLPF after 24 h of SD than after normal sleep, possibly representing some compensatory adaptations [91].

People may be differently affected in the same sleep-depriving environmental conditions. Recent data suggest that the brain responses to SD for a same task

are modulated by an individual vulnerability to SD [92]. In this study, subjects were divided into two groups, an SD-resilient group and an SD-vulnerable group, according to their performance at the SWMT after SD. On one hand, in the SD-resilient group, significant activations were found in several cortical areas (e.g., left DLPF, left VLPF, left SMA, left PPC) during practice of the SWMT after SD. On the other hand, only the left DLPF was found activated after SD in the SD-vulnerable group. The patterns of brain activation after SD may, therefore, differ as a function of one's vulnerability to SD [92].

All the above studies described the immediate consequences of SD on human performance in specific cognitive tasks. However, SD may also alter the slow processes leading to memory consolidation. Maquet and colleagues conducted an fMRI study to test this hypothesis [93]. The learning-dependent changes in regional brain activity after normal sleep or SD were compared using a pursuit task (PT), in which subjects were trained to hold a joystick position as close as possible to a moving target, whose trajectory was predictable on the horizontal axis but not on the vertical axis. The time on target was used as the behavioral performance parameter. In the first group, subjects were totally sleep deprived during the first post-training night, while in the second group, they were allowed to sleep. Both groups were then retested after at least two more nights, of normal sleep, in order to recover a similar state of arousal across the two groups and between the training and retest sessions. The fMRI scanning session was recorded during the retest, while subjects were exposed to the previously learned trajectory and also to a new one in which the predictable axis was vertical. Behavioral results showed that the time on target was larger for the learned trajectory than for the new one in both groups during the retest, and that this performance gain was greater in the sleeping group than in the SD group. The fMRI data showed a significant effect of learning, irrespective of the group, in two regions: the left supplementary eye field (SEF) and the right dentate nucleus (DN) (Fig. 3A). The right superior temporal sulcus (STS) was found more active for the learned than for the new trajectory, and more so in the sleeping group than in the SD group (Fig. 3B). The functional connectivity also showed that the DN was more closely linked to the STS, and the SEF to the frontal eye field (FEF), for the learned than for the new trajectory, and more so in the sleeping group (Fig. 3C). Moreover, interactions between temporal cortex and cerebellum as well as between the FEF and the SEF, are known to be both implicated in the standard pursuit eye movement pathways [94]. These results, therefore, suggest that the performance on the PT relies on the subject's ability to learn the motion patterns of trajectory in order to program the optimal pursuit eye movements. SD during the first post-training night would disturb the slow processes that lead to the acquisition of this procedural skill and alter the related changes in connectivity that are usually reinforced in subjects allowed to sleep [93].

Overall, functional imaging studies have described the early effects of SD on brain activity during practice of different cognitive tasks. These findings are of great interest because they may provide "baseline" models of brain responses to SD that could be used for clinical assessment in sleep disorders. For example, an efficient treatment could be expected to reverse some of the described SD-induced alterations in brain activity [81]. However, it should be mentioned that all the above studies were conducted on normal subjects and that sleep disorders may induce different functional patterns. Further studies are, therefore, needed to compare the brain responses to SD in normal subjects and in patients with a sleep disorder. Another major issue is that brain responses to SD seem to be highly variable, depending among others on the type of cognitive task, on its level of complexity and difficulty and on an individual vulnerability. These findings must be replicated and extended to have a reliable description of these modulating factors and their effects. Especially, the individual susceptibility to SD should be further documented, notably to explore its predicting factors and neurobiological mechanisms. Likewise, the proposed compensatory mechanisms underlying the post-SD activations should be reassessed in the light of new experimental data. Functional neuroimaging has also explored the impacts of SD on memory consolidation, for instance in a model of procedural learning. These results are akin to the experimental data supporting a role for sleep in leaning and memory [51,53–55].

3.2. Primary insomnia

Primary insomnia is characterized by inadequate sleep or poor sleep quality that is unrelated to other concomitant medical conditions [43]. Patients complain about difficulty falling asleep, difficulty maintaining sleep and/or early awakenings. As a result, they experience daytime dysfunction, including fatigue, mood symptoms, decreased attention, vigilance and concentration, but no objective sleepiness [95]. The prevalence of insomnia associated with daytime dysfunction ranges from 10% to 34% [96–100]. Persistent primary insomnia is associated with serious psychiatric and medical morbidities, as well as economic implications including loss of productivity, work-related accidents and absenteeism [101–104]. Quality of life is also greatly impaired [105]. Despite its high prevalence and serious consequences, the neurobiological basis of primary insomnia is still poorly understood. Up to now, there have been very few neuroimaging studies devoted to this disorder.

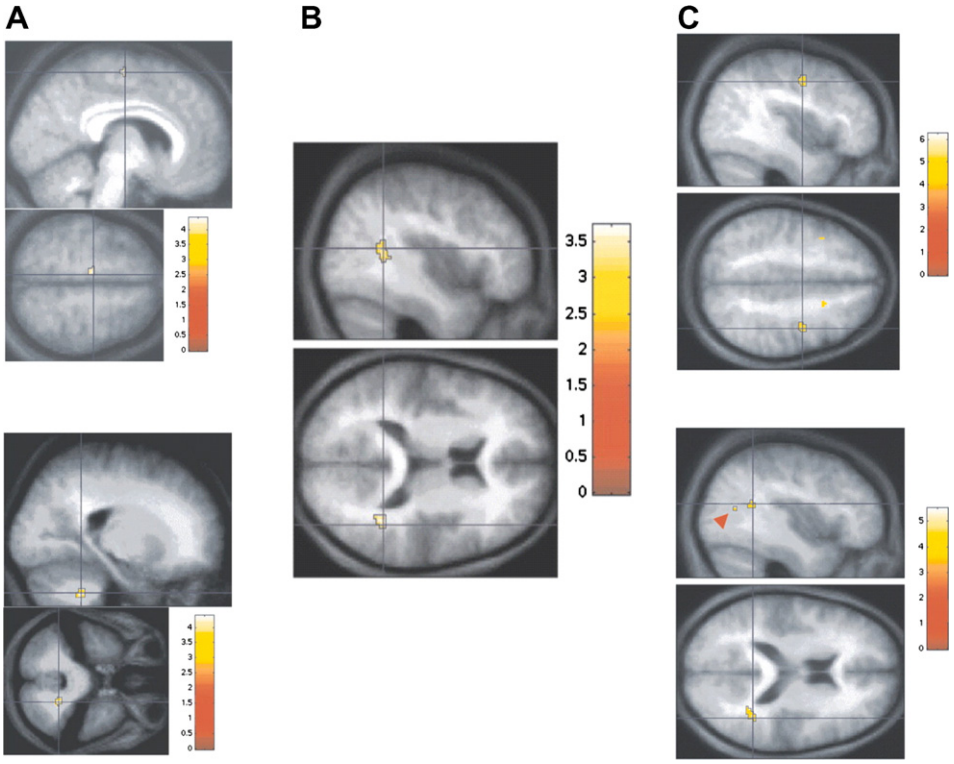

Fig. 3. Effects of sleep and sleep deprivation on pursuit task learning, assessed by fMRI [93]. (A) Main effect of learning. Activation foci (SEF on the upper panel; DN on the lower panel). (B) Trajectory by group interaction. The STS is significantly more active in the learned condition in sleeping subjects. (C) Results of the second-level analysis based on psychophysiological interactions. On the upper and lower panels, brain areas that are connected with the SEF and DN, respectively, more tightly for learned than new trajectories, and more so in sleeping subjects than in the sleep-deprived group. The red arrowhead shows a second area detected in the STS. These statistical results, displayed at $p < 0.001$, are coded according to the corresponding color scale and are superimposed on the average normalized structural magnetic resonance image of the group. Reprinted from The Journal of Neuroscience; vol. 23(4); Maquet P, Schwartz S, Passingham R and Frith C; "Sleep-related consolidation of a visuomotor skill: brain mechanisms as assessed by functional magnetic resonance imaging"; pp. 1432–40; Copyright 2003 by the Society for Neuroscience. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In a preliminary study, rCBF was assessed in five patients suffering from primary insomnia compared to four healthy good sleepers, using single-photon emission computed tomography (SPECT) with technetium-99m-hexamethylene-propyleneamine Oxime (Tc-99m-HMPAO), a gamma-emitting radionuclide imaging agent [104]. In patients compared to controls, significant rCBF decreases, but no increases, were found during the first non-REM sleep cycle in medial frontal, parietal and occipital cortices, with the largest reduction in the basal ganglia. In a second study, the same authors examined the effects of the behavior therapy (BT) on rCBF during non-REM sleep using the same technique [106]. Indeed, there is increasing evidence that BT is an effective treatment of insomnia [107], and the authors hypothesized a reversal of the previously reported patterns of cerebral deactivation [104] after the therapy. Accordingly, in preliminary results, they found a significant rCBF increase in the basal ganglia when comparing post- to pre-treatment [106]. However, these two studies suffer from several important limitations that restrict the interpretation of the results, including the small sample size (five patients in the first study, four in the second), and the lack of spatial resolution inherent to the HMPAO SPECT method.

Nofzinger and colleagues used the ^{18}FDG PET method to assess CMRGlu during wakefulness and non-REM sleep in seven primary insomnia patients and 20 healthy subjects [108]. The two groups had comparable electroencephalographic (EEG) sleep parameters, including the sleep efficiency which was surprisingly normal in the patients group. The results showed an increase in global CMRGlu during non-REM sleep in patients compared to controls. Insomniacs also displayed a smaller decline than controls in relative CMRGlu from wakefulness to non-REM sleep in the ascending reticular activating system, hypothalamus, thalamus, insula, amygdala, hippocampus, anterior cingulate and medial prefrontal cortices. During wakefulness, patients showed relative CMRGlu decreases in bilateral prefrontal, left hemispheric superior temporal, parietal and occipital cortices, the thalamus, hypothalamus and brainstem reticular formation compared to controls. These results show that sleep in insomnia

patients is associated with enhanced brain metabolism, which is in line with the concept of a ''hyperarousal'' state in insomnia [109]. They also suggest that difficulty falling asleep may be related to an abnormal progression of brain activity from waking to sleep states, in which there would be a failure to reduce activity in a general arousal system (ascending reticular formation, hypothalamus, thalamus), an emotion regulating system (hippocampus, amygdala, anterior cingulate cortex), and a cognitive system (prefrontal cortex). Lower prefrontal activity during wakefulness in insomniacs was finally interpreted as reflecting the subjective daytime fatigue resulting from inefficient sleep [81,108].

These neuroimaging data constitute the first attempts to provide a characterization of brain functional alterations underlying the pathophysiology of insomnia. However, these results must be interpreted cautiously, because they were based on a small number of insomnia patients, which considerably restricts their statistical significance. Further studies are needed to replicate and extend these findings in a larger sample of patients and, if possible, using other neuroimaging techniques allowing a better spatial and temporal resolution. Several additional questions should also be addressed in future neuroimaging studies dedicated to insomnia [110]. Firstly, the brain functional changes occurring during REM sleep and transitions from REM sleep to non-REM sleep or wakefulness still have to be described. Indeed, REM sleep is associated with alterations in limbic and paralimbic structures, which play an important role in emotion regulation, and alterations in emotional behavior have been reliably linked with insomnia complaints [111]. Secondly, taking into account the ''hyperarousal'' theory of insomnia, one should expect that processing of relevant or irrelevant stimuli during sleep elicits patterns of cerebral activity that are different in insomniacs compared to controls. Thirdly, it would be interesting to explore how the insomniac brain reacts to this chronic SD during the day, compared to normal subjects submitted to SD. Indeed, an intriguing fact is that, although insomniacs report presenting more subjective sleepiness during the day due to low sleep efficiency, only a small percentage of them actually have an objective pathological sleepiness [112]. Likewise, although they frequently complain of impairments in concentration, learning and memory, only a few scores of cognitive performance are significantly disturbed, mainly consisting of an alteration of long-term episodic memory [113]. The neural correlates of such a resistance to SD should be assessed. Fourthly, it is still unknown whether the different clinical presentations of insomnia, for example, primary insomnia and insomnia secondary to medical or psychiatric disorders, share common neurophysiological mechanisms. Neuroimaging studies conducted on a huge and heterogeneous insomnia population may help categorize this disorder on a pathophysiological basis, which may also influence the treatment. Finally, the effects of different types of treatments, such as pharmacological and BT, on brain functioning should be assessed and compared comprehensively, and might be later employed as a monitoring of efficacy [111].

3.3. Sleep-related breathing disorders

Obstructive sleep apnea (OSA) is a common disorder affecting up to 28% of the adult population [114] and is characterized by repeated complete or partial collapses of the upper airway during sleep [95]. These events cause reduction or cessation of airflow and lead to oxygen desaturation and repetitive micro-arousals. Micro-arousals and oxygen desaturation are thought to be responsible for excessive daytime sleepiness, fatigue, loss of mental flexibility, and altered attention and concentration, which are often experienced by patients with OSA. These decrements lead to reduced quality of life, impaired work performance, and increased risk of vehicular accidents.

The pathogenesis of OSA remains incompletely defined. Although abnormal upper airway anatomy leads to mechanic collapsibility, the occurrence and progression of OSA cannot be entirely explained by this single mechanism. Few neuroimaging studies have tried to find central nervous system abnormalities to explain the occurrence and symptoms of this pathology and controversial results have been found.

A first group of studies used MRI with the voxel-based morphometry (VBM) technique to assess the brain structural changes associated with OSA. Macey and colleagues reported on the presence of widespread, albeit often unilaterally distributed, gray matter losses in 21 patients compared to 21 controls [115]. Unilateral gray matter losses have been shown in regions such as the left ventro-lateral frontal cortex, anterior cingulate cortex and cerebellum, which are, respectively, brain structures involved in upper airway motor regulation, and potentially modulating cardiovascular and respiratory functions. Considering their unilateral distribution, associated with their occurrence in predominantly well-perfused sites, one should expect these lesions to be less susceptible to ischemic damage outcomes. Therefore, the authors speculated that these volume changes may have been present before the onset of OSA and may have contributed to a cascade of neural damage underlying this pathology. Conversely, they also reported a mainly diffuse and bilateral gray matter loss in the parietal and frontal cortex as well as a bilateral loss in the parahippocampal gyrus of the temporal lobe, suggesting that at least part of the damage would be a consequence of the repetitive and intermittent hypoxemic episodes. Damages to frontal, parietal and temporal regions were also proposed to contribute to cognitive

deficits frequently accompanying OSA [115]. Another group has published a VBM study on a smaller sample, demonstrating a gray matter volume deficit in the left hippocampus in seven patients with OSA compared to seven controls [116]. However, no significant changes were found in the rest of the brain. Finally, in a recent VBM study, O'Donoghue and colleagues [117] found no statistically significant gray matter changes in 27 patients with OSA compared with 24 control subjects. In particular, no differences were found in hippocampal volumes, contrasting with the previous reports [115,116]. The same group showed that six months of treatment with continuous positive airway pressure (CPAP) did not result in focal changes in gray matter concentration or in hippocampal or temporal lobe volume changes, although there was a small but significant decrease in whole brain volume [117].

Several studies used single voxel proton magnetic resonance spectroscopy (^{1}H-MRS) in order to assess the brain metabolic impairments potentially induced by cerebral hypoxemia in OSA. In a first study conducted in 25 patients, Kamba and colleagues [118] found a significant inverse relationship between the severity of OSA (assessed by the apnea-hypopnea index) and *N*-acetylaspartate (NAA)/choline (Cho) ratio in cerebral white matter. More recently, Alchanatis and colleagues demonstrated in 22 OSA patients a significant decrease in NAA/Cho and Cho/creatine ratios, as well as in absolute concentrations of NAA and Cho, in the frontal white matter when compared to 10 controls [119]. These results suggest that OSA induces axonal loss or dysfunction and myelin metabolism impairment, especially in the frontal white matter. Such frontal dysfunction may account for the OSA associated cognitive deficits, which mainly include executive functioning alterations, for instance the inability to initiate new mental processes and to inhibit automatic ones, deficits in working memory, analysis and synthesis and contextual memory [120–122]. Metabolic changes in gray matter have also been examined. Bartlett and colleagues found a decrease in creatine-containing compounds in the left hippocampal area in a small sample of patients (8 OSA compared to 5 controls) [123]. This decrease was correlated with worse OSA severity and neurocognitive performance (Psychomotor Vigilance Task [PVT]). Authors concluded that the hippocampus may be particularly vulnerable to hypoxic damage in OSA.

A few fMRI studies tried to characterize the brain correlates of the disturbed ventilatory control and underlying autonomic dysfunction in OSA. For instance, altered neural responses to Valsalva maneuver in eight OSA patients compared to 15 controls were shown in the inferior parietal cortex, superior frontal cortex, precentral gyrus, superior temporal gyrus, insula, cerebellum, hippocampus and anterior cingulate cortex [124]. These areas overlap with those where gray matter loss had been previously demonstrated [115] and include sites involved in motor control of diaphragmatic and upper airway muscles, sensory integration from the oral airway, blood pressure and breathing modulation [124]. The same group also found that a forehead cold pressor challenge elicited a disturbed sympathetic outflow and altered neural responses in limbic areas, cerebellum, frontal cortex and thalamus (10 OSA patients compared to 16 controls) [125]. Two other studies described the altered cerebral activity distribution during expiratory [126] and inspiratory [127] loading conditions in OSA.

Finally, a recent fMRI study has described the cerebral activations during executive function processing before and after CPAP treatment [128]. Practice of a two-back verbal working memory task induced activations in the DLPF, PPC and anterior cingulate cortex in a group of 10 healthy subjects, whereas it induced less extensive activations and a lack of significant DLPF involvement in a group of 16 OSA patients before treatment (Fig. 4, left panel), along with lower objective behavioral performances in the latter group. Lack of DLPF activation was not correlated with nocturnal hypoxia but seemed to rely mainly on sleep fragmentation. After a minimum of eight weeks of CPAP treatment, there was an improvement of subjective sleepiness scores contrasting with the absence of objective behavioral improvement and a persistent lack of DLPF activation in a group of six patients (Fig. 4, right panel). The authors concluded that there may be a dissociation between subjective clinical and objective behavioral/neurobiological recovery after treatment [128]. Using Tc-99m-HMPAO SPECT, Ficker and colleagues had previously found a marked frontal hyperperfusion in five OSA patients and a reduced perfusion in the left parietal region, changes that were reversed after effective CPAP [129]. As discussed above, a VBM study showed no local structural change after CPAP [117].

Mechanisms underlying OSA remain unclear. However, brain imaging studies offer the opportunity to foresee the possibility of primary cerebral dysfunction, responsible for the genesis and the progression of the OSA, coupled with secondary cerebral impairment, following repeated exposure to hypoxemia and/or sleep fragmentation, which would explain the cognitive symptoms encountered in this pathology. Thus, neuroimaging studies lead to a hypothesis that OSA would not be exclusively a consequence of anatomic factors. Existing studies must be replicated and extended on larger samples and state of the art techniques, in order to clarify these somewhat contradictory functional and structural changes. Future studies should continue to explore the neuro-psychological alterations and their neural correlates, by testing different cognitive modalities and assessing the respective contribution of hypoxia,

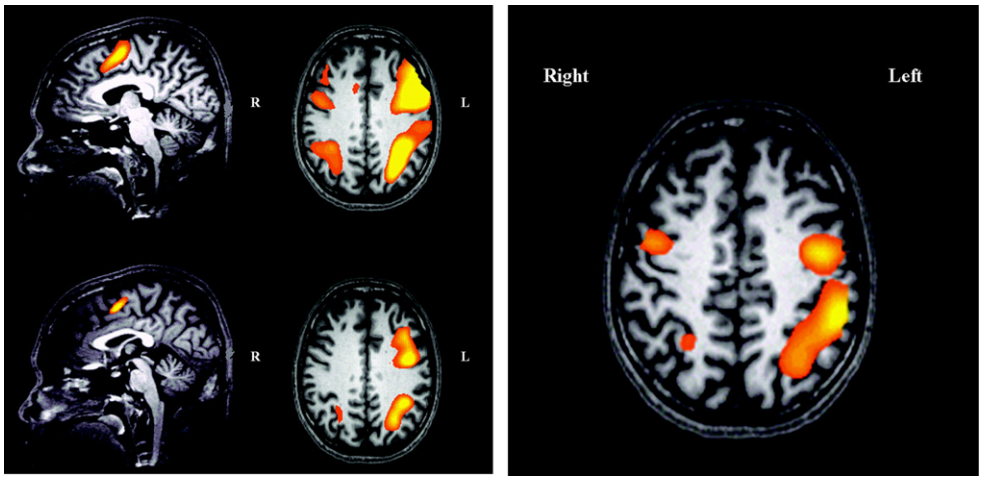

Fig. 4. An fMRI study of the effects of OSA on brain activation during a working memory task, before and after treatment with CPAP. (Left panel) Pre-treatment random effects group activation map of 16 patients with OSA, contrasted with 10 healthy subjects performing a similar working memory task. Activation in healthy subjects is more extensive, is bilateral, and involves PPC, medial wall in the region of the anterior cingulate cortex and DLPF (upper panel). OSA patients do not show significant DLPF activation but do so in left PPC and the medial wall (lower panel). R, right; L, left. All activations are Bonferroni corrected for multiple comparisons, $P < 0.05$. Talairach space z-coordinate is 30. Statistical color scale: red, $r = 0.4$; yellow, $r = 0.8$. (Right panel) Effect of treatment. Fixed-effects difference map for 6 patients after a minimum of 8 weeks of treatment with CPAP, associated with subjective resolution of symptoms. New areas of activation are seen especially in the posterior parietal cortex but not in the prefrontal areas, and objective performance remains unchanged. All activations are Bonferroni corrected for multiple comparisons, $P < 0.05$. Talairach space z-coordinate is 37. Statistical color scale: red, $r = 0.4$; yellow, $r = 0.8$. Reprinted from The Journal of Applied Physiology; vol. 98(6); Thomas RJ, Rosen BR, Stern CE, Weiss JW and Kwong KK; "Functional imaging of working memory in obstructive sleep-disordered breathing"; pp. 2226–34; Copyright 2005, used with permission from the American Physiological Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

respiratory events, arousals and sleep fragmentation or deprivation. Comparison with healthy SD subjects should also be explored, especially in the light of the previously proposed compensatory mechanisms [87]. To date, there is no neuroimaging data recorded during sleep itself in OSA. The study of neural activations and their time course around the occurrence of respiratory events during sleep should help refine the pathophysiology of OSA. The effects of treatment on brain function should be reassessed in order to clarify the reversibility level of cognitive and mood impairments, as well as its temporal dynamics (e.g., modulation by the earliness and duration of treatment). Neuroimaging tools could then be used to understand the neural basis of treatment efficacy, for instance by comparing responders and non-responders to CPAP. One could hypothesize that patients resisting to treatment may already have irreversible lesions or present some predisposing cerebral functional patterns. The pharmacological treatment of residual hypersomnia, despite CPAP use, should also be explored in terms of brain activity changes. Finally, the use of neuroimaging in OSA is still largely in its infancy. There are indeed several potential concerns at present that must be taken into account, such as the presence of associated medical conditions (e.g., arterial hypertension, diabetes, obesity, etc.) that may influence the brain responses, and restrictions imposed by technical settings (body weight, for example). The development of neuroimaging in OSA may, nevertheless, have important clinical applications in the prognosis, treatment and monitoring of this highly prevalent disorder.

3.4. Neurological disorders

3.4.1. Narcolepsy

Narcolepsy is a rare, life-long and disabling neurological disorder characterized by excessive daytime sleepiness (irresistible sleep attacks) and sudden drops of muscle tone (complete or partial) triggered by emotions, termed cataplexy [95]. A number of patients with narcolepsy also experience hypnagogic hallucinations and/or sleep paralysis. Nocturnal sleep disruption is typical in narcolepsy. Almost all patients with narcolepsy (and cataplexy) are positive for the human leukocyte antigen (HLA) subtype DQB1*0602, compared to the 12–38% of the general population who have this HLA subtype [130].

An anatomical or functional impairment of the pontine tegmentum, a region controlling the oscillations between sleep states, was first hypothesized as the main cause of narcolepsy. While Plazzi and coworkers [131] reported pontine tegmentum abnormalities (T2 hyperintensities) in their three patients with narcolepsy, using MRI, two other structural MRI studies [132,133] found no pontine abnormalities in idiopathic narcolepsy, except in 2 of 12 patients who had long-standing hypertension [133]. These lesions were indistinguishable from

ischemic changes and were associated with similar anomalies in the hemispheres. This suggests that MRI abnormalities found in the study of Plazzi and colleagues might also be the result of non-specific age-related pontine vascular changes. This phenomenon was described by Pullicino and coworkers [134]. More recently, since the discovery of substantial loss of hypocretin/orexin neurons in the lateral hypothalamus in canine and human narcolepsy [135–137], also shown by neuroimaging [138], research has focused on changes in cortical gray matter with VBM. Indeed, hypocretin neurons have widespread projections to numerous areas of the brain including the cortex [139]. While no differences were found between controls and patients with narcolepsy in one study [140], significant gray matter reductions were observed in inferior temporal and inferior frontal areas bilaterally in another [141] and reductions in right prefrontal and mesio-frontal cortex (but no reductions in temporal or hypothalamic regions) were observed in a third study [142]. The functional significance of these reductions remains highly speculative. For instance, they may contribute to some aspects of the reported attention-related cognitive deficits in narcolepsy [143].

As for neurotransmission, increased dopaminergic (DA) D2-receptor binding in the striatum was reported for human narcolepsy by post-mortem studies [144,145]. One SPECT study found that D2-receptor binding in the striatal DA system was increased and correlated with the frequency of cataplectic and sleep attacks in seven patients with narcolepsy [146]. However, opposite results were shown in other brain imaging studies using either PET [147,148] or SPECT [149], as they found no evidence of increased D2-receptor binding in narcolepsy. Other neurotransmitters were also investigated. For example, no change was found for the muscarinic cholinergic function, a main executive system for REM sleep, with PET using [11C]*N*-methyl-4-piperidyl-benzilate (^{11C}NMPB) [150].

There are also a few studies of cerebral metabolism or blood flow in narcolepsy. A ^{1}H-MRS study showed a decrease in the hypothalamic NAA/creatine-phosphocreatine ratio in 23 narcoleptic patients compared to 10 healthy controls, suggesting a neuronal loss or damage in the hypothalamus of these patients [151]. In a ^{18}FDG PET study, narcoleptic patients had reduced CMRGlu in several regions (e.g., bilateral rectal and subcallosal gyri, right superior frontal gyrus, right inferior parietal lobule, left supramarginal gyrus, and bilateral precuneus, posterior hypothalami and mediodorsal thalamic nuclei) compared to controls [152]. This segregated hypometabolism was proposed as underlying an impairment of hypothalamo-thalamo-cortical pathways in the pathophysiology of narcolepsy. The same group also conducted a technetium-99m-ethylcysteinate (^{99m}Tc-ECD) SPECT study during wakefulness in 25 narcoleptics compared to 25 controls and found a significant hypoperfusion in bilateral anterior hypothalami, caudate nuclei, limbic system, pulvinar nuclei of thalami, parts of the DLPF and VMPF, parahippocampal gyri and cingulate gyri [153] (Fig. 5). The authors concluded that this distribution could reflect hypocretin-related dysfunctional pathways, striatal DA dysfunction, as well as clinical features of narcolepsy, such as emotional lability and attentional deficits.

Effects of treatment have also been considered. Two fMRI studies investigated the impact of psychostimulants on the cortical response to sensory stimuli in patients with narcolepsy compared to control subjects. In two patients with narcolepsy, amphetamine resulted in an increase in the extent of the activation induced by visual and auditory stimulation in primary and association sensory cortex, whereas it produced a small reduction for controls [154]. This finding remains difficult to interpret as the study was conducted in a very small sample of subjects. On the other hand, modafinil did not significantly change the mean stimulation-induced cortical activation level either in narcoleptics or in control subjects, although those with narcolepsy reported being more alert [155]. However, there was a significant negative correlation between the pre-drug activation level and the post-treatment change in activation, suggesting that modafinil might nonetheless modulate brain activation to external stimuli. Once again, the limited number of subjects (8 narcoleptics and 8 controls) restrains interpretation of the results.

Overall, neuroimaging studies do not yet contribute significantly to a coherent and comprehensive description of the pathophysiology of narcolepsy. Further studies using recent neuroimaging methods, and based on large samples, are needed to confirm and extend these first results. They should focus, for instance, on the neural basis of the clinical hallmarks of the disease, such as sleep attacks, cataplexy, hypnagogic hallucinations and sleep paralysis, which remains poorly described in humans. Once again, the brain functional alterations during sleep itself remain at present largely unknown and should be further documented with respect to the different sleep stages and sleep-specific physiological events. The neurobiological response to pharmacotherapy should also be addressed more comprehensively.

3.4.2. Restless legs syndrome (RLS)/periodic leg movements during sleep (PLMS)

Restless legs syndrome (RLS) is a common neurological disorder characterized by four defining features: (1) an urge to move, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement; and (4) the urge to move or

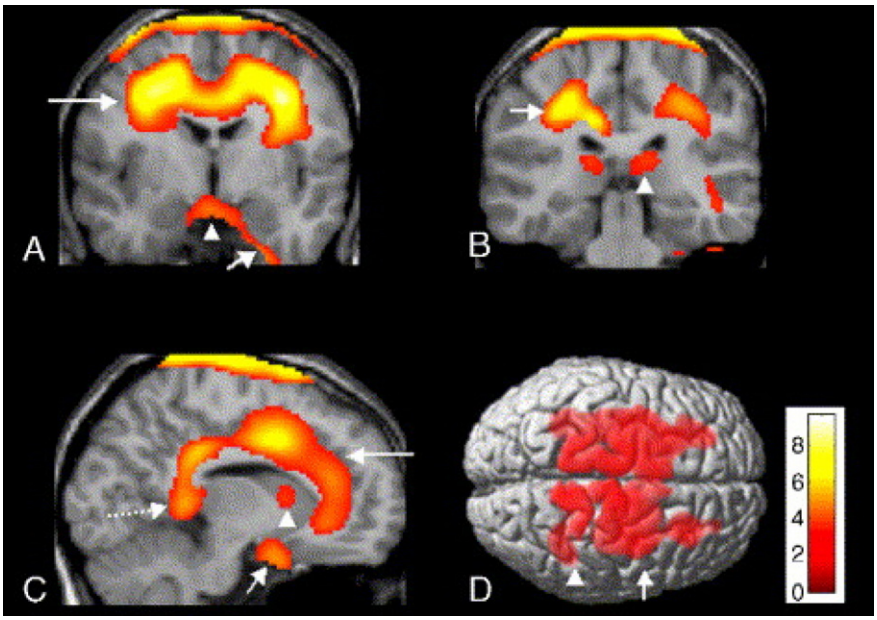

Fig. 5. Brain mapping of the regions where cerebral perfusion is decreased during wakefulness in narcoleptic patients compared to normal subjects. Cerebral perfusion was measured by ^{99m}Tc-ECD SPECT. Results are overlaid on T1 MRI. (A) Significant hypoperfusion was observed in bilateral anterior hypothalami (arrowhead) and in the right parahippocampal gyrus (short arrow). Bilateral cingulate gyri and white matters in bilateral middle frontal gyri (long arrow) showed decreased cerebral perfusion. (B) Hypoperfusion was evident in bilateral posterior thalami (arrowhead) and in the white matters of the bilateral postcentral and supramarginal gyri (short arrow). (C) In the sagittal view of right hemisphere, significant hypoperfusion was observed in the caudate nucleus (arrowhead), in the subcallosal gyrus (short arrow), the cingulate gyrus extending along corpus callosum (long arrow), and in the parahippocampal gyrus (dotted arrow). (D) Three-dimensional rendering view showing decreased cerebral perfusion in bilateral paracentral areas (arrowhead) and superior/middle frontal gyri (short arrow). The frontal lobe is on the right and the occipital lobe on the left. These results were significant at FDR-corrected $P < 0.05$. Reprinted from Neuroimage; vol. 28(2); Yeon Joo E, Hong SB, Tae WS, Kim JH, Han SJ, Cho YW, Yoon CH, Lee SI, Lee MH, Lee KH, Kim MH, Kim BT and Kim L. "Cerebral perfusion abnormality in narcolepsy with cataplexy"; pp. 410–6; Copyright 2005, with permission from Elsevier.

unpleasant sensations are worse in the evening or night than during the day, or occur only in the evening or night [156,157]. A great majority of patients with RLS also experience stereotyped repetitive movements once asleep, a condition known as periodic limb movements during sleep (PLMS) and also during wakefulness (PLMW). Typically, there is a positive family history of RLS and a positive therapeutic response to DA agents.

The primary cause of RLS is still unknown but therapeutic response of RLS and PLMS/PLMW to L-dopa and DA agonists have led to the hypothesis that central DA may be involved in the physiopathology of these conditions. Brain imaging studies using SPECT or PET investigated both the presynaptic DA transporter and postsynaptic D2-receptor binding in the striatum in order to pinpoint the deficit.

SPECT and PET studies on the presynaptic DA transporter, which reflects the number of DA neurons in the substantia nigra, all showed little or no change in transporter binding between patients with RLS and controls [158–162]. Presynaptic DA transporter binding was found to be negatively correlated with age in both patients with RLS and controls [159]. As for postsynaptic D2-receptor binding, the results are more inconsistent. Three SPECT studies [158,163,164] comparing RLS patients to age-matched controls failed to find a significant difference while another SPECT study [160] reported a small but statistically significant decrease in D2-receptor binding in patients with RLS. The only PET study with an adequate sample size (13 patients) also showed a small but significant decrease in striatal D2-receptor binding for raclopride in patients with RLS compared to controls [162]. No relationship was observed, however, between D2-receptor binding and either RLS severity or PLMS indices [160,162]. Overall, presynaptic DA transporter binding appears normal in patients with RLS contrary to what is typically found in early Parkinson's disease, suggesting that these two conditions do not share a common pathophysiology [159]. However, postsynaptic D2-receptor binding may be decreased, indicating a possible dysfunction or down-regulation of D2-receptors or alternatively increased levels of site occupancy by endogenous DA resulting from a increase in DA release [162]. Aside from pharmacological evidence, there is scant support so far for any significant DA abnormality in RLS. Unfortunately, only two RLS brain imaging studies [160,163] were performed in the evening when RLS symptoms are usually present. Future studies should

not only pay attention to when the brain imaging is performed, but also to how closely matched their patients with RLS and controls are for age, given the influence of age on DA neurotransmission [159].

Another possibility is that iron deficiency might be the primary cause of RLS. Indeed, iron is a co-factor for tyrosine hydroxylase that is the rate-limiting enzyme for DA synthesis [165]. Causes of secondary RLS are often related to an iron deficiency (pregnancy, uremia, blood donation) (for review, see [166]). Furthermore, a reduction in cerebrospinal fluid ferritin (and elevated transferrin) has been found in patients with idiopathic RLS [167]. In order to test this hypothesis, an MRI study was performed on a small sample (5 RLS patients and 5 controls), using a special measurement (R_2') that reflects regional brain iron levels [168]. It was found that brain iron concentration was significantly reduced in the substantia nigra and putamen (to a lesser extent) compared to controls and that, for both structures, the reduction was correlated with RLS severity as assessed by the John Hopkins RLS Severity Scale.

Finally, functional neuroimaging has also attempted to localize some cerebral generators of leg discomfort and PLMW in patients with RLS. An fMRI study (19 patients) showed a bilateral activation of the cerebellum and contralateral activation of the thalamus when patients with RLS experienced leg discomfort [169]. During the combined PLMW and sensory leg discomfort conditions, patients also showed activity in the cerebellum and thalamus with additional activation in the red nuclei and brainstem close to the reticular formation. In neither condition was any cortical activation found. However, when subjects were asked to voluntarily imitate PLMW, there was no activation in the brainstem, but rather additional activation in the globus pallidus and motor cortex. These results are in agreement with those of an EEG study showing no pre-movement cortical potentials for periodic leg movements during the daytime [170]. Altogether, these results support an involuntary mechanism of induction and a subcortical origin for RLS, as also suggested by a transcranial magnetic stimulation study [171].

Recently, a significant gray matter increase was found in the dorsal thalamus bilaterally (pulvinar) with T1-weighted MRI using VBM on a large sample (51 patients/51 controls) [172]. This is the first demonstration of structural changes in RLS and is in accordance with the increased activation of the thalamus during leg discomfort in patients with RLS, shown by Bucher and coworkers [169]. As the authors state, it remains to be determined whether this increase in gray matter reflects the pathogenesis of RLS or is the consequence of chronic increase in relevant afferent input.

In conclusion, some neuroimaging data support a dysfunction of cerebral DA neurotransmission and/or iron metabolism in the pathophysiology of RLS, in agreement with previous hypotheses. Larger studies, carried out with careful acquisition timing and subjects' selection, are needed to clarify their respective contribution. The studies attempting to characterize the potential brain sources of clinical features in RLS should also be pursued. In particular, not only waking events (e.g., leg discomfort, PLMW) but also sleep events (e.g., PLMS) should be explored with modern functional neuroimaging techniques. The description of the neural basis of these specific features should help answer intriguing questions such as the nosological significance of the periodic movements, which remains controversial.

3.4.3. Fatal familial insomnia (FFI)

This hereditary or sporadic disease is caused by a mutation at codon 178 of the prion-protein gene and manifests itself by insomnia, autonomic hyperactivation and motor abnormalities, leading invariably to a lethal outcome [173,174]. Two ^{18}FDG PET studies have been reported. The first one found an anterior thalamic hypometabolism in four awake patients with FFI, suggesting a thalamic dysfunction, which is corroborated by neuropathologic data [175]. A reduced glucose utilization in the thalamus was also evidenced in the second study conducted on seven patients, along with a mild hypometabolism in the cingulate cortex [176]. In six of the subjects, hypometabolism was also found in the basal and lateral frontal cortex, the caudate nucleus, and the middle and inferior temporal cortex. Among the seven patients, changes were actually more widespread in methionine/valine heterozygotes at codon 129, who had a longer symptom duration, compared to methionine/methionine homozygotes. Cerebral hypometabolism also correlated with the presence of protease-resistant prion protein. The authors conclude that hypometabolism in the thalamus and cingulate cortex is a common feature in FFI, while changes in other brain regions depend on several factors including the duration of symptoms. Formation of protease-resistant prion proteins may be the cause of neuronal dysfunction in this group of disorders [176]. Finally, in a more recent study, Kloppel and colleagues emphasized a possible involvement of serotoninergic neurotransmission in FFI [177]. They showed a reduced availability of serotonin transporters in a thalamus/hypothalamus region of two patients, using ^{123}I-beta-CIT SPECT. Obviously, the main limitation in the interpretation of these three studies is the very poor number of patients, related to the low prevalence of the disease. Multi-center studies are needed to gather a significant group of patients and confirm these results.

3.4.4. Kleine–Levin syndrome (KLS)

KLS is an exceptionally rare disorder, predominantly affecting adolescent males and characterized by recurrent episodes of hypersomnia and, to various degrees, behavioral or cognitive disturbances, compulsive eating behavior and hypersexuality [95]. Its pathophysiology remains largely unclear. Most neuroimaging data were obtained from single case studies [178–181]. Huang and colleagues recently reported SPECT findings in five patients [182]. They found a hypoperfusion in the thalamus bilaterally in all subjects during the symptomatic period that disappeared during the asymptomatic period. Perfusion reductions were also found in other regions (e.g., basal ganglia, frontal, temporal and occipital cortices) but only in part of the subjects during both periods. These data suggest a pivotal role for the thalamus in the hypersomnic periods of KLS patients [182]. Once again, replication on larger sample sizes is needed.

3.5. Parasomnias

According to the International Classification of Sleep Disorders [95], parasomnias are defined as "undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousals from sleep". Some of them are considered almost normal phenomena but others can result in injuries, sleep disruption or can be very disturbing for either the subject himself or his or her bed partner. Insights for effective management or treatments may come from the meticulous study of their pathophysiology. Brain imaging provided such data on some parasomnias which will be reviewed here.

3.5.1. Sleepwalking

Sleepwalking, or somnambulism, "consists of a series of complex behaviors that are usually initiated during arousals from slow wave sleep (SWS) and culminate in walking around with an altered state of consciousness and impaired judgment" [95]. It affects approximately 1–17% of children (at varying frequencies) and about 4% of adults. The only neuroimaging study of sleepwalking to our knowledge is that of Bassetti and collaborators [183] who studied, with ^{99m}Tc-ECD SPECT superimposed on MRI images, a 16-year-old man with frequent sleepwalking episodes. During the episode, an increase of 25% in rCBF was found in the posterior cingulate cortex (Brodmann area 23) and anterior cerebellum (vermis) compared to SWS without episodes. The authors draw a parallel between the functions of the cingulate cortex (modulating behavior in response to emotional processes) and the clinical characteristics of night terrors and sleepwalking. They do not, however, discuss the meaning of an anterior cerebellum involvement. Moreover, since it also occurs in normal SWS [1,3], the decreased CBF in frontoparietal associative cortices observed during the sleepwalking episode compared to awake normal subjects suggests that the brain is indeed sleeping during the episode while the body is in motion. This result then supports the notion of a dissociative state consisting of motor arousal and persisting mind sleep. It may also explain the lack of self-awareness, confusion, and amnesia typical of the somnambulistic episode [183]. These findings in a single case study need confirmation and replication on a significant sample.

3.5.2. Sleep terrors

Sleep terrors are defined as "arousals from SWS accompanied by a cry or piercing scream and autonomic nervous system and behavioral manifestations of intense fear... the person usually sits up in bed; is unresponsive to external stimuli and, if awakened, is confused and disoriented" [95]. A structural MRI report [184] of an adult-onset and video-polysomnography-confirmed case of sleep terrors showed increased T2 signal from the right thalamus suggestive of a low-grade tumor. A decrease of sleep spindles was also observed during non-REM sleep over the right hemisphere. A dysfunction of the thalamus may, therefore, contribute to the arousals during SWS leading to sleep terrors. The authors conclude that, while sleep terrors which typically occur in childhood are not associated with a neurological condition, an onset in adulthood could be indicative of a neurological disease. Larger samples and studies on primary sleep terrors are needed to assess these hypotheses.

3.5.3. REM sleep behavior disorder (RBD)

REM sleep behavior disorder (RBD) is characterized by the loss of skeletal muscle atonia usually present during REM sleep and involves complex motor activity occurring specifically in association with dream mentation. It was first described as a clinical entity in 1986 [185] and has a prevalence estimated at 0.5% [186], affecting mainly men over 50 years of age.

According to an early experimental model of RBD in the cat [187], the loss of muscle atonia during REM sleep and the corresponding "acting out" of oneiric behaviors would result from an impairment (lesion) of the mesopontine tegmentum. A structural MRI study of patients with RBD confirmed the hypothesized lesions in the dorsal mesopontine tegmentum in only three of six patients [188]. It showed, however, multifocal signal intensity lesions suggestive of lacunar infarcts in the periventricular white matter in five of the six patients. More recently, the mesopontine region was investigated by ^{1}H-MRS [189]. No significant differences were found between patients with RBD ($n = 15$) and age-matched controls on markers of neuronal loss or damage, membrane turnover impairment or abnormality in energy metabolism. The authors concluded that there was no marked neuronal loss in the mesopontine

tegmentum of patients with RBD, although they point out that the method used might not be sensitive enough to detect subtle abnormalities. An MRI and SPECT study was conducted on 20 patients with RBD [191]. Blood flow not only in the pons but also in the upper portion of the frontal lobe bilaterally was significantly lower in patients with RBD than in the normal elderly controls. Decreased blood flow in the frontal lobe of patients with RBD was not found to be correlated with the extent of their frontal lobe atrophy. Likewise, a decreased perfusion in the frontal lobes, but also in temporo-parietal cortices, was evidenced in a second SPECT study conducted in eight patients with idopathic RBD compared to nine control subjects [190]. However, this study also reported a paradoxical increased perfusion in the pons, putamen and right hippocampus. The authors argued that these functional patterns resembled those encountered in early stages of Parkinson disease, which would therefore support the concept of a common pathophysiologic mechanism for these syndromes at least in their initial stages [190].

Because RBD was frequently observed in association with Parkinson's disease and multiple system atrophy, conditions associated with an impairment of the central DA system, neuroimaging studies targeting directly the nigrostriatal DA system began to emerge in the year 2000. One of these studies [192] used SPECT in conjunction with a marker of the presynaptic DA transporter, [^{123}I] IPT, and a marker of postsynaptic D2 receptor density, [^{123}I] IBZM. It was found that all patients with RBD had reduced striatal DA transporters compared to age- and sex-matched controls, whereas the postsynaptic D2 receptor binding was not significantly different, similar to what was found in Parkinson's disease [193]. The same conclusions were reached by another research team [194] using PET imaging with a marker of vesicular monoamine transporter, [^{11}C] DTBZ. A reduction in binding was found in all striatal nuclei but was most marked in the posterior putamen. The striatal vesicular monoamine transporter density is actually considered to be a direct function of the number of DA neurons in the substantia nigra, therefore suggesting a loss of DA midbrain neurons in chronic RBD [194]. Another study [195] showed a significant reduction in striatal DA transporter binding from controls to patients with subclinical RBD (i.e., individuals who have REM sleep without atonia but without behavioral manifestations), from patients with subclinical RBD to clinical RBD and from patients with clinical RBD to patients with Parkinson's disease. This reduction was found to be correlated with the increase in long-lasting muscle activity during REM sleep in patients with subclinical RBD [195].

Future studies will have to confirm the respective roles of mesopontine tegmentum dysfunction and DA system impairment in the pathophysiology of RBD. Indeed, it is still unclear whether these alterations play a causal role or reflect consequences and adaptations to the pathological conditions. A role for other regions such as the frontal lobe should also be confirmed and explored. Finally, as only part of Parkinson patients develop or present RBD, other neurotransmitters than DA may be involved and should also be investigated.

3.5.4. Sleep-related bruxism

"Sleep related bruxism is an oral activity characterized by grinding or clenching of the teeth during sleep, usually associated with sleep arousals" [95], and which causes tooth wear, headaches, jaw dysfunction and pain. Its prevalence in adults has been estimated to be around 8% [196]. Although the presence of abnormal tooth wear is very indicative of sleep bruxism, a definite diagnosis relies on the presence of a certain level of rhythmic masticatory muscle activity and grinding sounds in an all-night polysomnographic recording. The orofacial morphology of sleep bruxers does not differ from that of controls [197].

In order to elucidate whether a DA impairment could be responsible for sleep bruxism as it is for other movement disorders (e.g., RLS/PLMS, Tourette's syndrome, Parkinson's disease, progressive supranuclear palsy and now RBD), a study of the regional cerebral D2 receptor density has been conducted with [^{123}I] IBZM SPECT [198]. Although no statistically significant difference was found between 10 subjects with bruxism and 10 controls for the mean striatal D2 binding potential, the inter-hemispheric difference in binding was greater in bruxers than in controls. A unilateral D2 receptor deficit had been described in idiopathic spasmodic torticollis, another movement disorder [199]. It could be hypothesized that an asymmetry in striatal DA function may be involved in the pathophysiology of certain movement disorders. It is worth mentioning, however, that no relationship was found in the study by Lobbezoo and coworkers [198] between the asymmetry values and bruxism severity. Further studies are needed to confirm this asymmetric DA system hypothesis. The associated brain functional and morphological changes should also be explored using recent neuroimaging techniques, in order to identify other possible generators of these abnormal movements during sleep.

3.6. Psychiatric disorders: sleep brain imaging in depression

The most frequent primary diagnosis in insomniac patients is depression [200]. Depression is characterized by a global decrease of pleasure, cognition and volition. Typical sleep features are associated with depression, such as insomnia and, less frequently, excessive sleepiness [95]. Sleep disturbances, a distinct symptom cluster comprised in the Hamilton Depression Rating Scale, correlated positively, during wakefulness, with glucose

metabolism in limbic structures and basal ganglia of depressed patients as measured by ^{18}FDG PET [201]. Links between these sleep disturbances and depression remain, however, incompletely understood.

There seems to be a bilateral influence between sleep and depression [202]. On one hand, sleep disturbances are consequences of depression. On the other hand, chronic insomnia is a risk factor for the development of depression. Moreover, there are persisting sub-clinical sleep EEG alterations in patients at risk for a depressive episode. Thus, regulation of sleep and regulation of mood seem to be closely linked.

Depressed patients have modifications of their sleep architecture characterized by reduced SWS, early onset of the first episode of REM sleep, and increased phasic REM sleep [203]. The spatial extent of anterior paralimbic activation from waking to REM sleep was shown to be greater in depressed patients [204]. Transition from wakefulness to non-REM sleep, in depressed patients, was characterized by relatively persistent "elevated" activity in fronto-parietal regions and thalamus [205]. This can be interpreted in several ways. A hyperarousal state during wakefulness may imply a lower decrease of brain activity from wakefulness to non-REM sleep. Alternatively, a low frontal metabolism during wakefulness may be no further decreased during non-REM sleep [205].

At present, the most comprehensive pathophysiological theory of depression actually relies on the hyperarousal hypothesis. When getting to sleep, depressed patients may experiment cognitive and emotional hyperarousal states which manifest themselves by persistent and worrying mental activity. Furthermore, physiological arousal has been described in depressed patients (e.g., increased heart rate) [206]. Since hyperarousal has also been described in insomnia, this may be a common pathway underpinning the close relationship between sleep and mood disorders [206]. Several arguments from neuroimaging support the concept that a high degree of brain activity (hyperarousal) during wakefulness is a crucial feature of depression. For instance, bupropion, an antidepressant drug, decreases brain metabolism during wakefulness [207], and sleep deprivation may allievate depression symptoms by decreasing abnormally elevated activity in the anterior cingulate cortex during wakefulness [208,209]. Sleep deprivation actually has rapid beneficial effects on about 60% of depressed patients [210]. Responders to sleep deprivation are usually patients with high behavioral activation and low levels of tiredness [211,212], which is in agreement with the increased arousal theory [206,213]. Brain functional imaging during sleep has also assessed relationships between hyperarousal and depression. In a ^{18}FDG PET and EEG study [214], beta power during non-REM sleep, a proposed electrophysiological marker of arousal, was negatively correlated with subjective sleep quality both in normal and depressed subjects. However, depressed patients exhibited a trend toward greater beta power than normal controls. Interestingly, beta power during non-REM sleep was correlated in both groups with glucose metabolism levels in the VMPF, a region among the most deactivated during non-REM sleep in normal subjects (see above) [1,9]. The authors concluded that elevated function in the VMPF might contribute to dysfunctional arousal in depressed patients [81,214].

Relationships between sleep, insomnia and depression open a neurobiological window to the understanding of the pathophysiological mechanisms of depression. We anticipate that much insight will be gained in the near future with the use of novel neuroimaging techniques.

4. Conclusions and perspectives

Neuroimaging has significantly contributed to the understanding of sleep physiology in humans by describing the functional neuroanatomy of sleep stages, proposing brain correlates of dreaming features and showing cerebral reactivations during sleep of regions involved in prior learning. As yet, our knowledge about normal human sleep remains fragmentary and these first studies pave the way for future works that will benefit from the development of multimodal techniques such as combined EEG/fMRI. For instance, the specific extent of sleep contribution in learning and memory processes is still debated and deserves additional investigation.

In sleep pathology, neuroimaging findings can be classified into several subcategories. Firstly, the structural MRI studies and VBM technique looked for morphological changes associated with a specific disorder. Secondly, studies using PET/SPECT and radio-labeled compounds with receptor binding properties assessed dysfunction in neurotransmission, especially for the DA system. Thirdly, spectroscopy studies were designed to detect signs of neuronal loss or damage, membrane turnover impairment or abnormality in energy metabolism. Finally, regional brain activity reflected by changes in cerebral blood flow, glucose metabolism or Blood-Oxygen-Level-Dependent (BOLD) fMRI signal was compared between sleep-disordered patients and controls, in some cases in response to cognitive tasks or physiological maneuvers.

The large majority of these sleep pathology studies was not conducted during the disturbed sleep itself but during wakefulness and, therefore, misses an important part of the information. Reasons for this are diverse [215]. On one hand, functional neuroimaging is difficult to conduct during sleep. It requires an adjustment of the technical settings and the participant has to sleep during data acquisition in this very unusual environment, mak-

ing data difficult to obtain. On the other hand, clinical manifestations in sleep disorders are often unpredictable and transient, such that it is never guaranteed to catch the targeted events during the scanning session. Moreover, some of these manifestations induce large movements, which would obviously disturb the data acquisition. In the case of OSA, the increase in blood CO_2 may directly interfere with the BOLD signal detection. The other frequent limitations of the available neuroimaging studies in sleep disorders include small samples of patients and limited spatial/temporal resolution. Several findings were also contradicted by others, while the results of some studies have not yet been replicated and confirmed.

Nevertheless, some interesting contributions from neuroimaging have been obtained up to now in sleep medicine. For instance, neuroimaging has provided further evidence for a ''hyperarousal'' state in insomnia and depression [108,214]. Frontal, parietal and hippocampal gray matter losses [115,116] and altered prefrontal activation [128] may underlie the cognitive impairment encountered in OSA patients. Morphological [138] and glucose metabolism/CBF data [152,153] suggest a dysfunction in hypocretin-related pathways in narcolepsy. Preliminary data support a cerebral iron deficiency in RLS [168]. Finally, neurotransmission studies suggest a loss of DA midbrain neurons in RBD [194].

Overall, it seems clear that there is a critical need for further research using neuroimaging in the field of sleep medicine. Future studies should address the following objectives.

First, the study of the brain structural and functional changes in sleep disorders during wakefulness, correlated with behavioral and physiological parameters, should be pursued. A critical concern will be to distinguish between primary dysfunctions leading to the development of the disorder and consequences, for instance due to sleep disruption, secondary to the sleep pathology. This will help to understand for each disease the pathophysiology as well as the clinical presentation and subsequent impairment on daytime functioning.

Second, the comprehensive characterization of the mechanisms of sleep disorders, or at least the brain correlates of the sleep disruption and/or clinical hallmarks of these disorders, would preferentially need data acquisition during sleep itself. This will allow to study, for instance, the pathophysiology of the clinical manifestations of narcolepsy, such as sleep attacks, sleep paralysis and hypnagogic hallucinations. We have mentioned above some of the potential difficulties restricting neuroimaging studies during sleep.

Third, neuroimaging may contribute to shape the nosography of sleep disorders. For instance, insomnia covers a large variety of presentations that are usually classified according to the clinical observation and coexisting medical or psychiatric conditions. However, the different subcategories usually overlap, making this classification difficult and somewhat arbitrary. Neuroimaging could help classify different types of insomnia on a neurobiological basis, an approach that may be complementary to the clinical one.

Finally, the effects of treatment could also be assessed by neuroimaging. First attempts have been made with CPAP treatment in OSA [117,128,129], modafinil in narcolepsy [155] and BT in insomnia [106]. These studies should be replicated and extended, and different treatments should be compared, for instance BT and hypnotics in insomnia. This approach may be applied later on as a monitoring of therapeutic response.

The use of neuroimaging in sleep medicine is still in its infancy. Nevertheless, we predict that future studies, conducted with state of the art techniques, will contribute significantly to the understanding of the neural basis of sleep pathologies. The design of these studies will be indubitably influenced by findings from sleep research using other modalities in humans and in animals. In the past, for example, the discovery of the hypocretin system has changed the whole conception of research in narcolepsy, including in the neuroimaging field. Future studies will also have to gain in significance by gathering large numbers of patients. Altogether, these concerns raise the importance of closer collaborations among basic neuroscientist sleep researchers, sleep physicians and neuroimagers, as well as multi-center studies to increase the sleep-disordered population sample. This may finally give in the future the opportunity to use neuroimaging, in addition to the clinical and electrophysiological assessments, as a helpful tool to the diagnosis, differential diagnosis, classification, treatment and monitoring of sleep disorders in humans.

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