Neuroimaging in Normal and Abnormal Sleep

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Introduction

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

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

Second, neuroimaging may serve to better characterize the pathogenic mechanisms of sleep disorders, or at least their cerebral correlates [5]. This endeavor is hindered by the fact that, from the practical and methodological points of view, scanning patients during their sleep is not easy. However, alternative approaches are available, as the functional and structural consequences of these sleep disorders can also be assessed during wakefulness. For instance, voxel-based morphometry (VBM) analysis can be used to detect structural brain changes typical of specific sleep disorders. Likewise, cardiovascular regulation can be assessed by probing important reflexes (e.g., during the Valsalva maneuver).

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

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

Neuroimaging in Normal Human Sleep

Sleep profoundly impacts the activity of numerous physiologic systems (see, e.g., Kryger et al. [6]). PET, SPECT, or fMRI studies reviewed in this section have demonstrated that global and regional patterns of brain activity during sleep are remarkably different from those during wakefulness. These studies have also shown the persistence of brain responses to external stimuli during sleep, and plastic changes in brain activity related to previous waking experience.

Functional Neuroimaging of Normal Human Sleep

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

NREM Sleep

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

In animals, the cascade of events that generates NREM sleep oscillations by thalamo-neocortical networks is induced by a decreased firing in the activating structures of the brainstem tegmentum [7]. In agreement with animal data, humans' PET studies show that brainstem blood flow is decreased during light NREM sleep [14] as well as during SWS [14–17]. During light NREM sleep, the pontine tegmentum appears specifically deactivated, whereas the mesencephalon seems to retain an activity that is not significantly different from wakefulness [14]. In SWS, both pontine and mesencephalic tegmenta are deactivated [16].

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

The role of the cortex in the generation of NREM sleep oscillations is equally important but not yet fully understood [20], especially at the neuronal level. Electroencephalographic power density maps have revealed a relatively typical predominance of the delta frequency band in the frontal regions, whereas sigma power predominated over the vertex [21]. Human PET data similarly showed that the pattern of cortical deactivation was not homogeneously distributed throughout the cortex. As compared to wakefulness, the least active areas in SWS were observed in various associative cortices of the frontal (in particular the dorsolateral and orbital prefrontal cortex) and parietal, and to a lesser extent in the temporal and insular cortices [14, 15, 16, 22]. In contrast, the primary cortices were the least deactivated cortical areas [15]. Finally, a meta-analysis of our own data [19] showed a linear (inverse) relationship between EEG spectral power within the delta frequency band and rCBF in ventromedial prefrontal regions during NREM sleep in non-sleep-deprived normal subjects. This result suggests an important role of medial prefrontal cortices in the modulation of delta waves.

The reasons for this heterogeneous cortical distribution remain unclear. One hypothesis is that, since polymodal association cortices are the most active cerebral areas during wakefulness, and because sleep intensity is homeostatically related to prior waking activity at the regional level [23], these cortices might be more profoundly influenced by SWS rhythms than primary cortices [8].

The predominance of rCBF decreases in prefrontal regions may be functionally important since these cortical

regions are involved in mood regulation and in various cognitive functions (e.g., planning or probability matching) [24] that help adaptation of individual behaviors. Studies of the deleterious effects of sleep deprivation on human cognition also pointed to a high sensitivity of these association cortices to sleep deprivation (see later).

The previous functional brain imaging studies have compared periods or "blocks" of brain activity averaged over several tens of seconds or minutes between NREM sleep and wakefulness. Because hyperpolarization phases may predominate over these periods, the resulting picture emerging from these studies is decreasing brain activity during NREM sleep in the areas where slow oscillations are most prevalent. While NREM sleep is consistently characterized by a global and regional net decrease of brain activity over several seconds or minutes, the concept of NREM sleep as a stage of brain quiescence is not accurate, as we know from animal studies that NREM sleep is also characterized by transient bursts of neuronal discharge ("up" states) organized by NREM sleep oscillations. We conducted an event-related fMRI study during NREM sleep in normal non-sleep-deprived human volunteers and showed that the occurrence of the phasic sleep spindles was associated with increases of brain activity in a specific set of cortical and subcortical structures, including the thalamus, paralimbic areas, and superior temporal gyri [25]. Moreover, beyond this general activation pattern, we also demonstrated that slow and fast spindles could be differentiated in terms of their macroscopic hemodynamic responses: slow spindles were specifically associated with activation of the superior temporal gyrus, and fast spindles preferentially recruited hippocampal and sensorimotor cortical areas. Besides bringing further evidence that spindles can be divided in two biologically distinct subtypes, this study demonstrates that NREM sleep cannot be reduced to a state of sustained brain deactivation but is characterized by phasic increases in brain activity triggered by NREM sleep oscillations, such as spindles, in agreement with animal data.

Further support for this notion was obtained from another study from our group, this one evaluating brain activation in response to slow waves during NREM sleep [26]. Compared with baseline activation during deep sleep, slow waves were associated with significant activation in the inferior frontal gyrus, parahippocampal gyrus, precuneus, posterior cingulate cortex, brain stem (pons), and cerebellum. Higher amplitude slow waves (>140 μV) were more consistently associated with parahippocampal and brainstem activation [26]. This specificity of slow-wave regional recruitment, particularly in parahippocampal and prefrontal regions, may subserve a role of slow waves in sleep-dependent memory consolidation. In addition, the activation of pontine structures with slow waves suggests a change of firing rate—from a tonic to a phasic mode—in specific brainstem nuclei during NREM sleep, in agreement with recent animal data [27].

REM Sleep

REM sleep is characterized by desynchronized neuronal activity [28, 29] and, correspondingly, by high cerebral energy requirements [12] and blood flow [13, 30]. In this active but sleeping brain, some areas are particularly active, even more than during wakefulness, while others have lower than average regional activity.

PET studies have shown significant rCBF increases during REM sleep in the pontine tegmentum, thalamic nuclei, limbic and paralimbic areas, amygdaloid complexes [31, 32], hippocampal formation [15, 32], anterior cingulate cortex [15, 31, 32], and orbitofrontal and insular cortices [32] (Fig. 21.1). Posterior cortices in temporo-occipital areas were also found to be activated [15], although less consistently. In contrast, the inferior and middle dorsolateral prefrontal gyri, the inferior parietal cortex, and the posterior cingulate cortex and precuneus were the least active brain regions [15, 31].

Regional brain activity in subcortical mesopontine and thalamic regions during human REM sleep [14, 31] is in keeping with our current understanding of sleep generation in animals. REM sleep is generated by neuronal populations of the mesopontine reticular formation that activates the thalamic nuclei, which in turn activate the cortex [28].

Functional connectivity between remote brain areas is also modified during human REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory, is reversed during REM sleep [15, 33]. Likewise, the functional relationship between the amygdala and the temporal and occipital cortices is different during REM sleep than during wakefulness or NREM sleep [34]. This pattern suggests that functional interactions between neuronal populations are different during REM sleep than during wakefulness. A recent resting-state fMRI study demonstrated that REM sleep connectivity is also different from NREM sleep connectivity, specifically in the set of brain areas known as the default-mode network [35]. The default-mode network consists of regions activated when the brain is not engaged in externally oriented behavior [36]. The functional connectivity within the default-mode network is diminished in NREM sleep, but in REM sleep, it is comparable to that in wakefulness [35]. Moreover, in REM sleep, the higher-order association cortices (encompassing the default-mode network) engage in a rapid oscillatory fluctuation of anticorrelated activation with the sensorimotor areas [35]. These characteristic patterns of activation may underlie neuroplastic and phenomenal aspects of REM sleep.

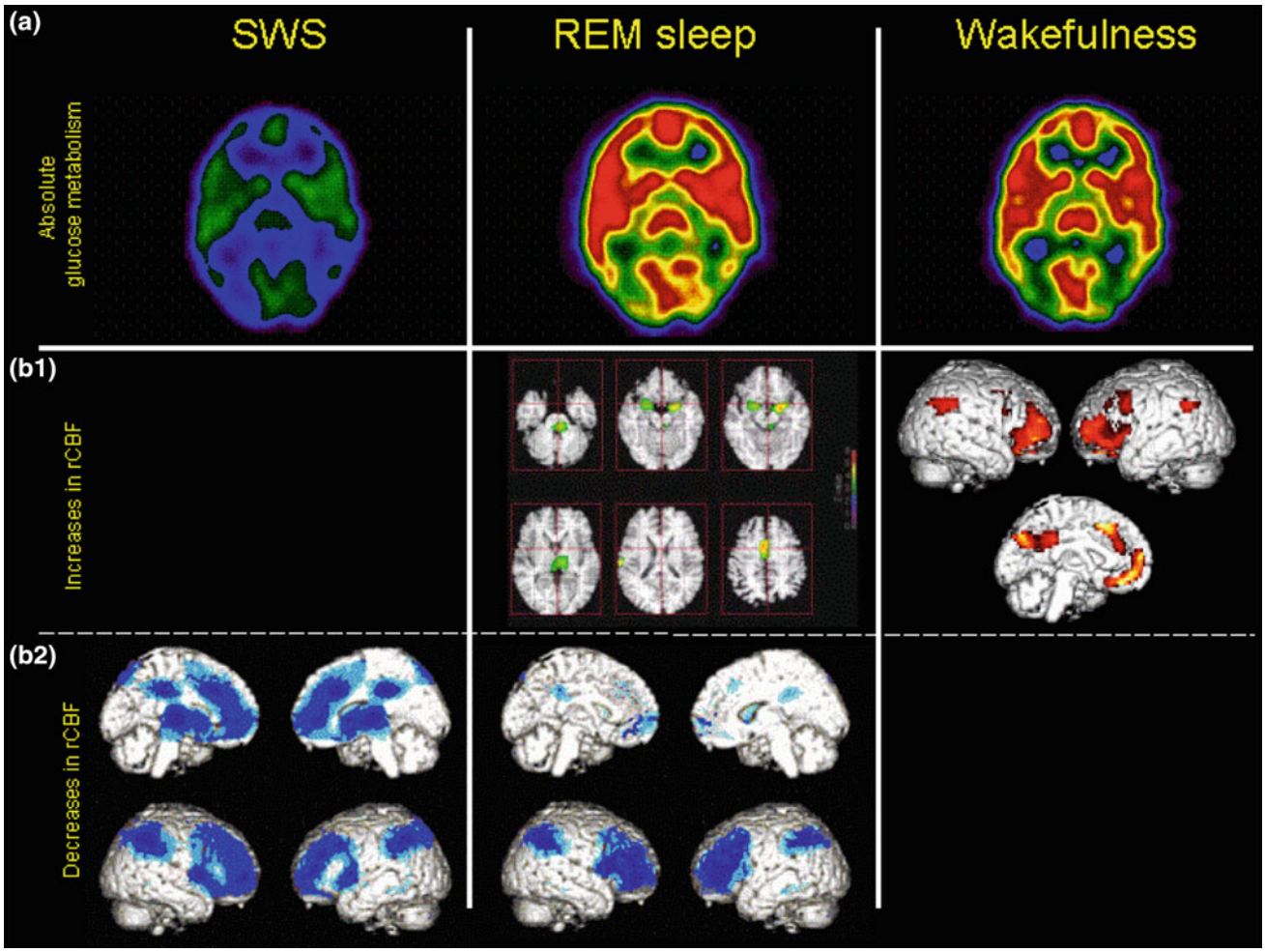

Fig. 21.1 Cerebral glucose metabolism (*CGM*) and regional cerebral blood flow (*CBF*) during deep NREM sleep (*first column*), REM sleep (*second column*), and wakefulness (*third column*). Row **a** CGM quantified in the same individual at 1-week interval, using FDG and PET. The three images are displayed at the same brain level using the same color scale. The average CGM during deep NREM sleep (versus wakefulness) is significantly decreased. During REM sleep, the CGM is as high as during wakefulness. Row **b1** Distribution of the *highest* regional brain activity, as assessed by CBF measurement using PET, during wakefulness and REM sleep. The most active regions during *wakefulness* are located in the polymodal associative cortices in the prefrontal and parietal lobes (both on the medial wall and convexity). During REM sleep, the most active areas are located in the pontine tegmentum, thalami, amygdaloid complexes, and anterior cingulate cortex. Other data (not shown) have shown a large activity in the occipital cortices, insula, and hippocampus [15]. Row **b2** Distribution of the *lowest* regional brain activity, as assessed by CBF measurement using PET, during NREM and REM sleep. In both sleep stages, the least active regions are located in the polymodal associative cortices in the prefrontal and parietal lobes (convexity). During NREM sleep, the brainstem and thalami are also particularly deactivated

Pontine waves, or ponto-geniculo-occipital (PGO) waves, are also primary features of REM sleep. In rats, the generator of the pontine waves projects to a set of brain areas shown to be active in human REM sleep: the occipital cortex, the entorhinal cortex, the hippocampus, and the amygdala as well as brainstem structures participating in the generation of REM sleep [37]. Although most easily recorded in the pons [38], the lateral geniculate bodies [39], and the occipital cortex in cats [40], PGO waves are also observed in many parts of the brain, including limbic areas (amygdala, hippocampus, cingulate gyrus) [41]. Several observations suggest that PGO waves also occur during human sleep. In epileptic patients, direct intracerebral recordings in the striate cortex showed monophasic or diphasic potentials during REM sleep, isolated or in bursts [42]. In normal subjects, surface EEG revealed transient occipital and/or parietal potentials time-locked to the REMs [43]. Source dipoles of MEG signal were localized in the brainstem, thalamus, hippocampus, and occipital cortex during REM sleep [44, 45]. Using PET, we showed that the rCBF in the lateral geniculate bodies and the occipital cortex is tightly coupled to spontaneous eye movements during REM sleep, but not during wakefulness [46]. This finding has been confirmed by fMRI studies [47, 48]. Although fully conclusive

components are still awaited, these elements support the hypothesis that PGO-like activities participate in shaping the distribution of regional brain activity during human REM sleep.

Many subjective aspects of dreams may be related to changes in brain activation during REM sleep [49], as evidenced by a series of PET studies. Increased perfusion in the occipital and temporal lobes, in the absence of afferent sensory input, may relate to the visual and auditory experiences that characterize dreams [33]. Indeed, lesions in the occipital cortex are associated with suppressed visual mentation during dreams. Increased perfusion in the motor and premotor areas during REM sleep may relate to movement perception in dreams [8, 15]. These intended movements are not physically enacted because efferent motor signals are suppressed in REM sleep by muscle atonia. This suppression can be inhibited by pontomedullary lesion, as has been shown in cats. Lesioned cats then engage in coordinated movement during REM sleep, ostensibly acting out their dreams. Similar behavior is also observed in humans with REM sleep behavior disorder (RBD) (see section below). The amygdala is particularly active during REM sleep [15, 31], perhaps underlying the potent emotions experienced in dreams. Regional deactivations during REM sleep are also related to certain elements of dreams. The lateral prefrontal cortex, an area involved in the monitoring of complex cognitive processes during waking, shows marked hypoperfusion during REM sleep [8]. Accordingly, dreams are often characterized by a bizarreness and incoherence of which the dreamer is unaware. The failure to coherently access episodic memory during dreams is also attributable to lateral prefrontal deactivation. In contrast, the medial prefrontal cortex remains activated in REM sleep. The representation of others' minds, known as theory of mind, is a function thought to be subserved by this area, and indeed, dreams contain characters with thoughts, emotions, and intentions of their own. However, the delimitation of the dreamer's mind is less distinct. Dreamers commonly move between first-person and third-person perspectives over the course of a dream. The inability to differentiate first- and third-person perspective may be associated with decreased perfusion in the inferior parietal cortex [50].

Recently, Dresler et al. [51, 52] were able to image lucid dreaming, a rare and intriguing feature of REM sleep. Unlike in normal dreams, lucid dreamers can gain awareness of the fact that they are dreaming, can access long-term memory stores, and can willingly control the events of their dream. Moreover, lucid dreamers can, to a slight extent, control their real eye and hand movements while maintaining polysomnographic sleep. By instructing the dreamer to provide gestural signals at the onset of a lucid dream, researchers determined that several areas normally deactivated in normal dreaming become activated during lucid dreaming, including the dorsolateral prefrontal cortex [51]. In a related experiment, Dresler et al. [52] asked participants to perform a pretrained motor task during lucid dreaming. They found that similar areas were activated during the dreamed mentation of a motor task and during its execution in wakefulness. It should be noted that both of these studies are limited by very small samples of 1 or 2 participants, owing to the rarity of lucid dreaming.

Brain Reactivity to External Stimulation During Sleep

Electrophysiologic studies have demonstrated that sleep is not a state of complete unresponsiveness to external stimuli (e.g., Perrin et al. [53]). Early studies have shown that external stimuli can induce an autonomic or electrophysiologic response during human sleep, in particular after a relevant or meaningful stimulus presentation [54]. Available PET and fMRI data globally suggest that the processing of external stimuli can proceed beyond the primary cortices during NREM sleep. However, the mechanisms by which salient stimuli can recruit associative cerebral areas during sleep remain unclear. A pioneering fMRI study found that, during NREM sleep as during wakefulness, several areas continue to be activated by external auditory stimulation: the thalamic nuclei, the auditory cortices, and the caudate nucleus [55]. Moreover, the left amygdala and the left prefrontal cortex were found to be more activated by subjects' own names than by pure tones, suggesting the persistence during sleep of specific responses for meaningful or emotionally laden stimuli.

Other groups observed that auditory stimulation induced a decreased response in the auditory cortex [56, 57]. Intriguingly, visual stimulation during SWS in adults elicited a decrease in activity in the occipital cortex [58]. This decrease was more rostral and dorsal compared to the relative rCBF increase along the calcarine sulcus found during visual stimulation in the awake state. The origin of this negative blood oxygenation level is still unclear [59]. One fMRI study investigated responsiveness to sounds during REM sleep, and detected auditory cortex activation during tonic but not phasic REM sleep. The non-responsiveness observed in phasic REM sleep was interpreted as a state of functional isolation [60].

Processing of external stimuli during sleep may be dependent on spontaneous brain activity, such as sleep spindles. In order to explore this interaction, we conducted an EEG/fMRI study involving the presentation of pure tones

to participants sleeping in the scanner [61]. When comparing blood-oxygen-level-dependent (BOLD) activation from tones presented during and outside of sleep spindles, we found a stark difference in global activation. Whereas tones played outside of spindles elicited activation in the thalamus and auditory cortex, replicating earlier results [55], tones played during spindles produced no significant activation, save for a small area in the brainstem [61]. These results show that sleep spindles effectively hinder the transmission of external auditory stimulation to the cortex during NREM sleep. This finding may explain variable susceptibility to noise disturbance during sleep, within and between subjects. Indeed, in another study, sleep stability in the presence of auditory disturbance was correlated with spindle density [62]. The "noise-canceling" function of sleep spindles is also consistent with its hypothesized role in sleep-dependent memory consolidation, in that it may contribute to brain functional isolation necessary for endogenous information processing in the absence of contaminating inputs. In support of this notion, hippocampal connectivity with neocortical areas was increased during sleep spindles, suggesting information transfer akin to systems consolidation [63]. In the same EEG/fMRI study, we also investigated the interaction between incoming auditory stimulation and K-complexes. It was found that sound-induced K-complexes were associated with increasing activation in the auditory cortex [61]. This finding suggests that K-complexes reflect a facilitated processing of sensory information at the cortical level during NREM sleep. Finally, in a complementary study, we examined the effect of slow-wave phase on the processing of auditory stimulation in NREM sleep [64]. We found a larger activation of the superior temporal gyrus with sounds presented during the up state of the slow wave compared to those presented during the down state. Therefore, the processing of sensory stimulation during NREM sleep is closely regulated by the underlying state of neural synchronization and firing, as reflected by slow waves and spindles.

Sleep and Brain Plasticity

Evidence accumulates suggesting that sleep participates in the consolidation of recent memory traces [65]. Accordingly, PET studies have shown that waking experience influences regional brain activity during subsequent REM and NREM sleep. Several brain areas, activated during procedural motor sequence learning (using a serial reaction time task) during wakefulness, have been found to be significantly more activated during subsequent REM sleep in subjects previously trained on the task than in non-trained subjects [66]. Furthermore, this effect is not observed in subjects trained to a task with similar practice requirements but devoid of any sequential content [67]. These findings speak against use-dependent changes in regional brain activations. Additionally, functional coupling between learning-related areas was found to be enhanced during post-training REM sleep [68]. Another PET study demonstrated that hippocampal and parahippocampal areas, which are activated during a spatial memory task, can be reactivated during post-training NREM sleep and that the amount of hippocampal activity during SWS positively correlated with overnight improvement in the memory for spatial locations [69]. Collectively, these findings suggest that reactivations of regional activity and modifications of functional connectivity during post-training sleep reflect the off-line processing of recent memory, which eventually leads to improved performance the next day. Moreover, these results are in line with behavioral data suggesting that NREM sleep and REM sleep differentially modulate the consolidation of declarative and non-declarative memories, respectively [70, 71]. However, they do not rule out an alternative hypothesis that natural succession of NREM sleep and REM sleep is also mandatory for memory consolidation.

Functional MRI studies demonstrated that sleep deprivation hinders the plastic changes that normally would occur during post-training sleep [72]. In this study, the effects of normal sleep or sleep deprivation on learning-dependent changes in regional brain activity were assessed after the subjects were trained on a pursuit task, in which they had to hold a joystick position as close as possible to a moving target, whose trajectory was predictable on the horizontal axis but not on the vertical axis. The time on target was used as the behavioral performance parameter. In the first group, subjects were totally sleep-deprived during the first post-training night, while in the second group, they were allowed to sleep. Both groups were then retested after 2 more nights of normal sleep in order to recover a similar state of arousal across the two groups and between the training and retest sessions. The fMRI scanning session was recorded during the retest, while subjects were exposed to the previously learned trajectory and also to a new one in which the predictable axis was vertical. Behavioral results showed that the time on target was larger for the learned trajectory than for the new one in both groups during the retest and that this performance gain was greater in the sleeping group than in the sleep deprivation group. The fMRI data showed a significant effect of learning, irrespective of the group, in two regions: the left supplementary eye field and the right dentate nucleus. A region of the right superior temporal sulcus, close to regions coding for motion processing (biologic motion, smooth pursuit, etc.), was found to be more active for the learned than for the new trajectory, and more so in the sleeping group than in the sleep deprivation group. The functional connectivity also showed that the dentate nucleus was more closely linked to the superior temporal sulcus, and the

supplementary eye field to the frontal eye field, for the learned than for the new trajectory, and more so in the sleeping group. Moreover, interactions between the temporal cortex and cerebellum, as well as between the frontal eye field and the supplementary eye field, are both known to be implicated in the standard pursuit eye movement pathways [73]. These results therefore suggest that the performance on the pursuit task relies on the subject's ability to learn the motion characteristics of trajectory in order to program optimal motor pursuit execution. Sleep deprivation during the first post-training night would disturb the slow processes that lead to the acquisition of this procedural skill and alter related changes in functional connectivity that were reinforced in subjects allowed to sleep [72].

Orban et al. [74] used fMRI in order to map regional cerebral activity during place-finding navigation in a virtual town, immediately after learning and 3 days later, in subjects either allowed regular sleep (RS) or totally sleep-deprived (SD) on the first post-training night. Results showed that, at immediate and delayed retrieval, place-finding navigation elicited increased brain activity in an extended hippocampo-neocortical network in both RS and SD subjects. Moreover, behavioral performance was equivalent between groups. However, striatal navigation-related activity increased more at delayed retrieval in RS than in SD subjects. Furthermore, correlations between striatal response and behavioral performance, as well as functional connectivity between the striatum and the hippocampus, were modulated by post-training sleep. Overall, these data suggest that brain activity is restructured during sleep in such a way that navigation in the virtual environment, initially related to a hippocampus-dependent spatial strategy, becomes progressively contingent in part on a response-based strategy mediated by the striatum. Interestingly, both neural strategies eventually relate to equivalent performance levels, indicating that covert reorganization of brain patterns underlying navigation after sleep is not necessarily accompanied by overt changes in behavior [74]. Further studies have also evidenced a reorganization of brain activity when post-training sleep is allowed both for neutral [75] and emotional [76] verbal material, as well as for visual face-to-location associations [77]. In addition, exposure to an odor during SWS that had been presented as context during prior learning improved the retention of hippocampus-dependent declarative memories and elicited a significant hippocampal activation during SWS [78]. In a similar experiment using sounds to cue object-location memory, it was also shown that functional connectivity between the parahippocampal region and the visual cortices was enhanced upon sound presentation during SWS [79].

In addition, EEG and MEG studies have provided robust evidence for the "sleep and memory consolidation" hypothesis by focusing on more specific sleep features and mechanisms that are regarded as important for different types of memory, including sleep spindles [80–83], slow waves [84], or the actual number of rapid eye movements [85]. For instance, sleep homeostasis has a local synaptic component, which can be triggered by a learning task involving specific brain regions. The local increase in slow-wave activity after learning correlated with improved performance of the task after sleep [84]. Moreover, the induction of slow oscillation-like potential fields by transcranial application of slowly oscillating potentials (0.75 Hz) during early nocturnal NREM sleep (i.e., a period of emerging SWS) enhanced the retention of hippocampus-dependent declarative memories in healthy humans. This stimulation induced an immediate increase in SWS, cortical slow oscillations, and slow spindle activity in the frontal cortex [86].

Sleep spindles appear to play a central role in NREM sleep-dependent memory consolidation. Specifically, spindles appear to organize the concerted reactivation of neocortical areas involved in a memory with its hippocampal trace. In this way, spindles are believed to facilitate the transfer of newly consolidated memories from the hippocampus to the neocortex. Accordingly, Bergmann et al. [87] demonstrated in an EEG-fMRI study that sleep spindles were temporally coupled with concurrent activation in the hippocampus and neocortical areas relevant to a previously learned declarative memory task. Notably, this spindle-hippocampo-neocortical synchrony was greater after declarative learning than after a visuomotor control task and was correlated with performance on the declarative task. Furthermore, the magnitude of hippocampo-neocortical activation was proportional to variations in spindle amplitude. The key role of sleep spindles in memory consolidation is consistent with its aforementioned ability to block out external stimulation during NREM sleep [61].

Alertness, Performance, and Sleep Deprivation

Sleep deprivation or fragmentation is increasingly common in industrialized societies (noisy environments, shift work). Likewise, many sleep disorders are common in the general population (e.g., insomnia, anxiety disorders). The considerable proportion of vehicle accidents related to sleep loss is now viewed as a serious concern for public health [88]. The impact of sleep deprivation on cognition and brain functions has been assessed mainly in healthy subjects. By comparison, studies on the consequences of sleep disorders on behavior and cerebral activity remain scarce.

Cognitive Challenges

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

An early PET study with [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG) investigated the effect of total sleep deprivation (about 32 h) on brain metabolism [89]. Although global brain metabolism was not affected by sleep deprivation, regional glucose metabolism significantly decreased in the thalamus, basal ganglia, and cerebellum. A significant reorganization of regional activity was observed after sleep deprivation, with relative decreases in the cerebral metabolic rate of glucose (CMRglu) within the temporal lobes and relative increases in the visual cortex [89]. Additionally, sleep deprivation significantly reduced performance in an attentional continuous performance test, and this decrease was significantly correlated with reduced metabolic rate in thalamic, basal ganglia, and limbic regions [89].

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

The same group of researchers characterized the cerebral effects of 24, 48, and 72 h of sleep deprivation during the same task performance in 17 healthy subjects using correlations with performance measures outside of the scanner and metabolism during resting state assessed by ^{18}FDG PET [90]. Results showed that absolute CMRglu and relative regional CMRglu decreased further at 48 and 72 h of sleep deprivation primarily in the prefrontal and parietal cortices and in the thalamus, the same areas that showed decreases at 24 h of sleep deprivation. The authors proposed that the decreases in CMRglu induced in the prefrontal-thalamic network by sleep deprivation underlie the progressive impairment in cognitive performance and alertness and the progression toward sleep onset. In contrast, increased activity in visual and motor areas would reflect voluntary attempts to remain awake and perform despite a continuing decline in prefrontal-thalamic network activity [90].

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

Drummond and colleagues used fMRI on normal subjects while those subjects performed different cognitive tasks after a normal night of sleep or following 35 h of sleep deprivation. In a first report [4], the study used a serial subtraction task. Bilateral activations in the prefrontal, parietal, and premotor cortices were found during task practice after a normal night of sleep, whereas activity in these regions declined markedly after sleep deprivation, mainly in the prefrontal cortex [4], which is in agreement with the hypothesis of prefrontal cortex vulnerability to sleep deprivation [91]. Likewise, Mu et al. [92] found reduced activations in several frontal and parietal regions (left dorsolateral prefrontal cortex, right ventrolateral prefrontal cortex, supplementary motor area, Broca's area, and bilateral posterior parietal cortices) during practice of the Sternberg working memory task after 30 h of sleep deprivation compared to normal sleep. However, a very different pattern emerged when using other types of tasks. For example, the effects of 35 h of continuous wakefulness on cerebral activation during verbal learning (memorizing a list of words) were also investigated using fMRI [93]. The authors found that the prefrontal cortex and parietal lobes were more activated during verbal learning after 1 night of sleep deprivation than after normal sleep. In addition, increased subjective sleepiness in SD subjects correlated significantly with the amount of prefrontal cortex activation, while stronger parietal lobe activation was linked to less impairment in the free recall of words. Neurobehavioral (fMRI) effects of 24 h of continuous wakefulness were assessed using two verbal working memory tasks of different difficulty levels, known to induce responses in frontal-parietal networks in normal, non-sleep-deprived conditions. After sleep deprivation, activity was reduced in the medial parietal, anterior medial frontal, and posterior cingulate regions in both tasks, and disproportionately greater activation of the left dorsolateral prefrontal cortex and bilateral thalamus was observed when additional manipulation of information in working memory was required [94] (see also [95]). It has been suggested that these results reflect dynamic, compensatory changes in cerebral activation during verbal learning after sleep deprivation [93]. Compensatory mechanisms may lead to stronger responses within regions typically underlying task performance, as well as to activation in regions that do not show significant responses to task demands in the well-rested condition [96]. Indeed, the thalamus was also found to be

hyperactivated in sleep deprivation during a visual attention task, in the absence of performance deficits [97]. In another fMRI study, performance on a higher-order attention task was unaltered by sleep deprivation, while greater thalamic activation was recruited in the SD group [98]. The thalamus may thus play an important role in cognitive compensation in SD states.

These data suggest that decreases in regional brain activity could contribute to cognitive impairment after sleep deprivation and that increased prefrontal and thalamic activation may represent compensatory adaptation. In a similar attempt to better understand how sleep deprivation might interact with task difficulty, an fMRI study found stronger correlation between difficulty in a logical reasoning task and increased activity in the bilateral inferior parietal lobes, bilateral temporal cortex, and left inferior and dorsolateral prefrontal cortex following 35 h of continuous wakefulness than after normal sleep [96]. In a second study by the same group, the effects of normal sleep and 36 h of total sleep deprivation were assessed by fMRI during a verbal learning task with two levels of difficulty (easy and difficult words) [99]. A set of regions showed increased response to difficult words after sleep deprivation compared with normal sleep (inferior frontal gyrus, dorsolateral prefrontal cortex, and inferior parietal lobe, bilaterally). While better free recall performance on the difficult words following sleep deprivation was positively related to activation within the left inferior and superior parietal lobes and left inferior frontal gyrus, it was negatively related to activation within the right inferior frontal gyrus. Consequently, the performance relationships are thought to be both beneficial (as a compensatory function) and deleterious (as an interference with task performance), depending on the brain regions implicated. In addition, these studies suggest that increased recruitment of compensatory brain regions is yoked to rising task difficulty.

The default-mode network appears to be compromised by sleep deprivation. Disengagement of these brain regions is thought to be necessary for optimal externally oriented cognitive performance, and disturbances in default-mode function are observed in mental disorders [100]. According to a few recent studies, typical task-related default-mode network suppression was disrupted after sleep deprivation [101] and functional connectivity between default-mode areas was compromised [102, 103]. Furthermore, the anti-correlation between the default-mode network and its externally oriented counterpart was weakened in the SD condition [102].

Other cognitive domains seem to be impaired by sleep deprivation. For instance, competent decision making was impaired after sleep deprivation, which induced a modulation of activation in the nucleus accumbens and insula, brain regions associated with risky decision making and emotional processing [104]. Likewise, SD healthy adults were more likely to adopt risky strategies in a gambling task, and this change correlated with ventromedial prefrontal activation and anterior insular deactivation [105]. Furthermore, the ventromedial prefrontal and ventral striatum showed greater activation during wins, and the anterior cingulate displayed smaller deactivation during losses. These data indicate that the pursuit of gain is amplified in sleep deprivation, while losses are perceived more optimistically. Another fMRI study deprived participants of REM sleep only or NREM sleep only and evaluated emotional reactivity in a visual emotional reactivity task [106]. They found emotional reactivity to be enhanced in the REM-deprived group only, concurrently with increased activity in occipital and temporal areas, compared to NREM-deprived controls. The authors conclude that emotional reactivity is modulated by REM sleep.

Since prefrontal cortex functioning appears to be affected by sleep loss, processes mediated by this region should be altered after sleep deprivation (e.g., attention, emotion, motivation, feeding, and olfaction). In order to assess the effects of sleep deprivation on olfaction, which is mediated by the orbitofrontal cortex, a region known to have decreased activity after sleep deprivation [2], Killgore and McBride [107] studied 38 healthy subjects at rest and after 24 h of sleep deprivation. Relative to rested baseline performance, SD subjects showed a significant decline in the ability to identify specific odors on the Smell Identification Test. In relation to effects on feeding, an fMRI study examined BOLD response to the presentation of images of food items after a night of sleep deprivation [108]. Activation of the anterior cingulate cortex in response to food was increased in sleep-deprived participants with respect to non-sleep-deprived controls, independent of prescan blood-glucose levels. Moreover, this activation correlated significantly with increased post-scan hunger ratings. Sleep deprivation thus seems to enhance hedonic response to food stimuli.

Changes in dopamine neurotransmission may underlie the cognitive challenges observed in sleep deprivation. Dopamine's involvement in sleep/wake regulation remains unclear, but degeneration of dopamine pathways is associated with sleep disorders such as REM sleep behavior disorder and excessive daytime sleepiness in Parkinson's disease (PD) [109, 110]. In a series of studies, Volkow et al. [111–113] studied the effect of sleep deprivation on dopamine using PET with ^{11}C-raclopride, a dopamine D_2/D_3 receptor radioligand. They found dopamine receptor occupancy to be increased in the ventral striatum. Furthermore, this increase does not seem to be due to changes in dopamine transporter (DAT) density [114]. Increases in dopaminergic activity were associated with worse performance on a visual attention task, concurrent with BOLD changes in known dopamine-modulated areas (smaller

deactivation of anterior cingulate cortex and insula) as well as in other areas (greater deactivation of inferior occipital cortex and cerebellum) [112]. These findings suggest that striatal dopamine hyperactivity may interfere with attentional processes, or instead, may represent a compensatory mechanism in order to maintain arousal after sleep deprivation.

Personal Vulnerability to Sleep Deprivation

People may be differently affected by the same sleep-depriving environmental conditions. Studies suggest that brain responses to sleep deprivation for a given task are modulated by individual vulnerability to sleep deprivation [115]. For example, in one fMRI study, subjects were divided into two groups, a sleep deprivation-resilient group and a sleep deprivation-vulnerable group, according to their performance on a working memory task after sleep deprivation. In the sleep deprivation-resilient group, significant activations were found in several cortical areas (left dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex, left supplementary motor area, and left posterior parietal cortex) during practice of the working memory task after sleep deprivation. By contrast, in the sleep deprivation-vulnerable group, only the left dorsolateral prefrontal cortex was activated after sleep deprivation. The patterns of brain activation after sleep deprivation may therefore differ as a function of the subjects' individual vulnerability to sleep deprivation [115]. The same group conducted another fMRI study on fatigue vulnerability in military pilots. Pilots were scanned during the working memory task under non-sleep-deprived conditions, and individual fatigue vulnerability was quantified using performance on a flight simulation during 37 h of continuous wakefulness. Analyses revealed that global cortical activation during the working memory task was positively correlated with fatigue resistance in flight-simulator performance. The authors therefore proposed that baseline fMRI activation during the working memory task may provide a good index of individual fatigue susceptibility [116].

Individual differences in the effect of sleep deprivation on working memory performance were assessed by fMRI in 26 healthy volunteers, in a rested condition and after 24 and 36 h of sustained wakefulness [117]. In both sleep deprivation conditions, task-related activation was significantly decreased with respect to the rested condition in the superior parietal regions and left thalamus. There was also an inverse correlation between activation of left parietal and left frontal regions during the rested condition, and individual decline in working memory performance from the rested condition to the 24-h sleep deprivation condition. In this way, frontoparietal activation in the rested state may distinguish individual cognitive vulnerability to sleep deprivation. Similarly, another fMRI study showed that lower task-related activation of the ventral prefrontal cortex during rested wakefulness was predictive of greater individual ability to maintain inhibitory efficiency in a go/no-go task [118]. Low-vulnerability individuals also showed reduced activation in this region as well as in the right insula after sleep deprivation, compared to highly vulnerable individuals.

In addition to functional imaging, structural neuroimaging techniques were also used to investigate interindividual differences in responses to sleep deprivation. For instance, studies of white matter anatomy with fractional anisotropy (FA) may provide one such physiologic marker of vulnerability to sleep deprivation [119]. In that study, West Point cadets first completed a simple visual-motor task before and after 24-h sleep deprivation and their change in performance was assessed. Taking these change scores as indices of sleep deprivation vulnerability, cadets were separated into a more vulnerable and a less vulnerable group by median split. They were then scanned with MRI using diffusion tensor imaging (DTI), and FA was calculated for each cadet as an indicator of fiber number, density, and myelination in white matter tracts. FA values were significantly greater in the low-vulnerability group than in the high-vulnerability group, predominantly in ascending and longitudinal pathways of the right hemisphere and the genu of the corpus callosum. Furthermore, greater FA values correlated significantly with smaller decreases in the performance on the task. These findings are consistent with those of aging studies linking greater white matter integrity to improved cognitive performance [120].

Sleep Deprivation in Depression

Sleep deprivation has profound effects on brain metabolism in both normal and depressed subjects. When used therapeutically (i.e., wake therapy), sleep deprivation relieves acute depressive symptoms in 60 % of patients. In depressed patients responding favorably to sleep deprivation, ^{18}FDG PET [121–123], technetium-99m–labeled hexamethylene-propyleneamine oxime (^{99m}Tc-HMPAO) SPECT [124, 125], and fMRI [126] revealed greater baseline brain activity during wakefulness in responders than in non-responders in the anterior cingulate cortex and/or the nearby mesial frontal cortex. This activity was significantly decreased after sleep deprivation. A similar profile of brain metabolism was observed with ^{18}FDG PET in elderly depressed patients, including normalization after total sleep deprivation associated with antidepressant treatment [127]. Moreover, the normalization of anterior cingulate metabolism persisted even after recovery sleep. However, these results were not replicated with placebo control [128].

MRI spectroscopic studies have shown glutamate [129, 130] and serotonin [131] levels to be globally increased after sleep deprivation in depressed patients. These neurotransmitters may then underlie the antidepressant effect of sleep

deprivation. This is consistent, in the case of serotonin, with the widespread use of selective serotonin reuptake inhibitors as antidepressants. With PET and SPECT, it was also shown that sleep deprivation responders exhibit a significant decrease in relative basal ganglia D_2 receptor occupancy after sleep deprivation, as compared to non-responders [132]. Sleep deprivation also resulted in lower binding of ^{11}C-raclopride, a D_2/D_3 receptor radioligand, in the striatum and thalamus of healthy subjects [111]. These results suggest that the antidepressant benefits of sleep deprivation are correlated with enhanced endogenous dopamine release in responders, although a later study suggests DAT downregulation may instead be responsible for observed increases in dopamine receptor occupancy [113]. Nonetheless, these results corroborate previous hypotheses about the role of dopaminergic response in the therapeutic action of sleep deprivation and indirectly support a dopamine hypothesis of depression [132]. In relation to this hypothesis, sleep-deprived healthy subjects reacted more intensely to pleasure-evoking stimuli in dopaminergic mesolimbic brain networks associated with reward [133]. In addition, gains produced higher ventromedial prefrontal and ventrostriatal activation in healthy subjects, and losses produced less anterior cingulate deactivation [105]. Together, these findings suggest that the antidepressant effect of sleep deprivation may operate through reward-enhancing increases in dopaminergic activity.

^{31}Phosphorous magnetic resonance spectroscopy (^{31}P-MRS) has also been applied to healthy SD participants to understand the metabolic and bioenergetic changes that may underlie the antidepressant effect of wake therapy. Within-subject designs with healthy participants showed no change in phosphate brain chemistry after a night of sleep deprivation [134, 135], although one study found elevated β-nucleoside triphosphate and reduced phospholipid catabolism after a subsequent recovery night [134]. In a sample of depressed women, higher baseline levels of choline compounds in the pons were associated with the improvement in mood after sleep deprivation, indicating a role of pontine choline metabolism in the antidepressant response to sleep deprivation [136]. Further studies are needed scanning both depressed patients and healthy controls before and after sleep deprivation.

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

Instrumental Manipulation of Sleep Deprivation Effects

Repetitive transcranial magnetic stimulation (rTMS) can be used to artificially stimulate cortical brain areas, enabling true experimental designs in human neuropsychology. Luber et al. [137] used rTMS to artificially relieve impairments in working memory performance from sleep deprivation. Fifteen participants were first scanned with fMRI before and after sleep deprivation, while completing a working memory task. The brain areas that showed deactivation under sleep deprivation were then used as guides for rTMS application after a second night of sleep deprivation, two weeks later. Of the three identified sites, stimulation of the upper middle occipital site produced improvements in performance, whereas no improvement was accrued from the other sites or from sham rTMS. Furthermore, the degree of performance enhancement was directly proportional to the magnitude of each participant's sleep-deprivation-induced deactivations. Hence, cognitive deficits from sleep deprivation can be corrected with rTMS by targeting the affected brain area. The authors replicated these findings in a recent experiment [138].

Summary

There is a marked heterogeneity in the functional findings relating to the cognitive effects of sleep deprivation. Deficits in cognitive function after sleep deprivation have been correlated with both activations and deactivations in several brain regions. Hypotheses explaining these findings range from compensatory mechanisms in order to maintain cognitive function, to homeostatic pressure diverting energy from certain regions, resulting in cognitive deficits. These hypotheses remain speculative. The wide range of tasks employed in these studies may in part explain the variability in results. Nonetheless, some interesting markers of individual vulnerability to sleep deprivation have been identified, including white matter integrity. In addition, the study of the therapeutic effect of sleep deprivation in depression has yielded some promising findings, particularly in relation to the dopaminergic system. Lastly, sleep deprivation effects can seemingly be rectified by the targeted use of rTMS.

Neuroimaging in Sleep Disorders

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

In this section, we consider several primary sleep disorders (narcolepsy, periodic limb movement disorder, idiopathic insomnia, recurrent hypersomnia, and obstructive sleep apnea) as well as specific parasomnia syndromes

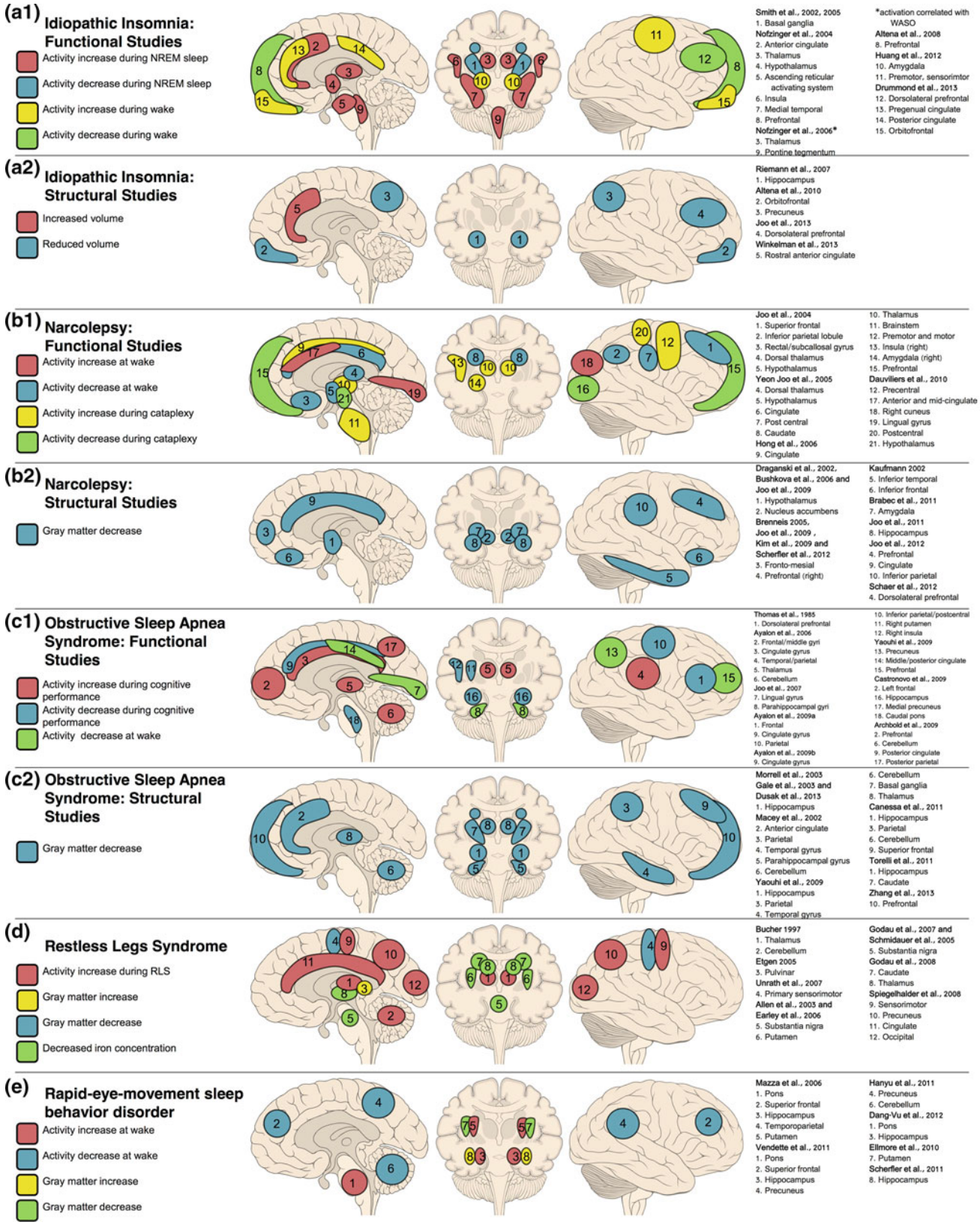
(a1) Idiopathic Insomnia: Functional Studies
Activity increase during NREM sleep
Activity decrease during NREM sleep
Activity increase during wake
Activity decrease during wake
Smith et al., 2002, 2005
1. Basal ganglia
Nofzinger et al., 2004
2. Anterior cingulate
3. Thalamus
4. Hypothalamus
5. Ascending reticular activating system
6. Insula
7. Medial temporal
8. Prefrontal
Nofzinger et al., 2006*
3. Thalamus
9. Pontine tegmentum
*activation correlated with WASO
Altena et al., 2008
8. Prefrontal
Huang et al., 2012
10. Amygdala
11. Premotor, sensorimtor
Drummond et al., 2013
12. Dorsolateral prefrontal
13. Pregenual cingulate
14. Posterior cingulate
15. Orbitofrontal
(a2) Idiopathic Insomnia: Structural Studies
Increased volume
Reduced volume
Riemann et al., 2007
1. Hippocampus
Altena et al., 2010
2. Orbitofrontal
3. Precuneus
Joo et al., 2013
4. Dorsolateral prefrontal
Winkelman et al., 2013
5. Rostral anterior cingulate
(b1) Narcolepsy: Functional Studies
Activity increase at wake
Activity decrease at wake
Activity increase during cataplexy
Activity decrease during cataplexy
Joo et al., 2004
1. Superior frontal
2. Inferior parietal lobule
3. Rectal/subcallosal gyrus
4. Dorsal thalamus
5. Hypothalamus
Yeon Joo et al., 2005
4. Dorsal thalamus
5. Hypothalamus
6. Cingulate
7. Post central
8. Caudate
Hong et al., 2006
9. Cingulate
10. Thalamus
11. Brainstem
12. Premotor and motor
13. Insula (right)
14. Amygdala (right)
15. Prefrontal
Dauvilliers et al., 2010
12. Precentral
17. Anterior and mid-cingulate
18. Right cuneus
19. Lingual gyrus
20. Postcentral
21. Hypothalamus
(b2) Narcolepsy: Structural Studies
Gray matter decrease
Draganski et al., 2002,
Bushkova et al., 2006 and
Joo et al., 2009
1. Hypothalamus
2. Nucleus accumbens
Brenneis 2005,
Joo et al., 2009 ,
Kim et al., 2009 and
Scherfler et al., 2012
3. Fronto-mesial
4. Prefrontal (right)
Kaufmann 2002
5. Inferior temporal
6. Inferior frontal
Brabec et al., 2011
7. Amygdala
Joo et al., 2011
8. Hippocampus
Joo et al., 2012
4. Prefrontal
9. Cingulate
10. Inferior parietal
Schaer et al., 2012
4. Dorsolateral prefrontal
(c1) Obstructive Sleep Apnea Syndrome: Functional Studies
Activity increase during cognitive performance
Activity decrease during cognitive performance
Activity decrease at wake
Thomas et al., 1985
1. Dorsolateral prefrontal
Ayalon et al., 2006
2. Frontal/middle gyri
3. Cingulate gyrus
4. Temporal/parietal
5. Thalamus
6. Cerebellum
Joo et al., 2007
7. Lingual gyrus
8. Parahippocampal gyri
Ayalon et al., 2009a
1. Frontal
9. Cingulate gyrus
10. Parietal
Ayalon et al., 2009b
9. Cingulate gyrus
10. Inferior parietal/postcentral
11. Right putamen
12. Right insula
Yaouhi et al., 2009
13. Precuneus
14. Middle/posterior cingulate
15. Prefrontal
Castronovo et al., 2009
2. Left frontal
16. Hippocampus
17. Medial precuneus
18. Caudal pons
Archbold et al., 2009
2. Prefrontal
6. Cerebellum
9. Posterior cingulate
17. Posterior parietal
(c2) Obstructive Sleep Apnea Syndrome: Structural Studies
Gray matter decrease
Morrell et al., 2003
Gale et al., 2003 and
Dusak et al., 2013
1. Hippocampus
Macey et al., 2002
2. Anterior cingulate
3. Parietal
4. Temporal gyrus
5. Parahippocampal gyrus
6. Cerebellum
Yaouhi et al., 2009
1. Hippocampus
3. Parietal
4. Temporal gyrus
6. Cerebellum
7. Basal ganglia
8. Thalamus
Canessa et al., 2011
1. Hippocampus
3. Parietal
6. Cerebellum
9. Superior frontal
Torelli et al., 2011
1. Hippocampus
7. Caudate
Zhang et al., 2013
10. Prefrontal
(d) Restless Legs Syndrome
Activity increase during RLS
Gray matter increase
Gray matter decrease
Decreased iron concentration
Bucher 1997
1. Thalamus
2. Cerebellum
Etgen 2005
3. Pulvinar
Unrath et al., 2007
4. Primary sensorimotor
Allen et al., 2003 and
Earley et al., 2006
5. Substantia nigra
6. Putamen
Godau et al., 2007 and
Schmidauer et al., 2005
5. Substantia nigra
Godau et al., 2008
7. Caudate
8. Thalamus
Spiegelhalder et al., 2008
9. Sensorimotor
10. Precuneus
11. Cingulate
12. Occipital
(e) Rapid-eye-movement sleep behavior disorder
Activity increase at wake
Activity decrease at wake
Gray matter increase
Gray matter decrease
Mazza et al., 2006
1. Pons
2. Superior frontal
3. Hippocampus
4. Temporoparietal
5. Putamen
Vendette et al., 2011
1. Pons
2. Superior frontal
3. Hippocampus
4. Precuneus
Hanyu et al., 2011
4. Precuneus
6. Cerebellum
Dang-Vu et al., 2012
1. Pons
3. Hippocampus
Ellmore et al., 2010
7. Putamen
Scherfler et al., 2011
8. Hippocampus

Fig. 21.2 Findings from PET, SPECT, fMRI and MRI studies in sleep disorders. **a1** Brain areas showing metabolic changes in idiopathic insomnia. Most studies show hypermetabolism in cortical and subcortical areas during NREM sleep, as well as smaller decreases in metabolism in the transition from wake to sleep. These results are consistent with the hyperarousal theory of insomnia. During wake, insomnia patients show decreased prefrontal activity. **a2** Neuroanatomical alterations in idiopathic insomnia. While many studies found no anatomic changes in insomnia patients, some reported cortical gray matter loss or changes in hippocampal or rostral anterior cingulate volume. **b1** Areas showing functional abnormalities in narcolepsy. All metabolic and hemodynamic changes are shown during wake, and one study imaged hypoperfusions during a cataplectic episode. Abnormalities in narcoleptics were reliably observed in the hypothalamus, consistent with a hypocretinergic dysfunction. **b2** Neuroanatomical alterations in narcolepsy. Hypothalamic gray matter loss may relate to hypocretinergic dysfunction. Limbic and neocortical alterations may underlie mood disturbances in narcoleptic patients. **c1** Functional studies on OSAS have focused mainly on activity changes during cognitive tasks and have mostly detected deactivations. A few resting-state studies using PET and SPECT have found decreases in activity during resting wakefulness. **c2** Neuroanatomical alterations in OSAS. Gray matter loss in the hippocampus, parietal, and prefrontal cortices may underlie various neuropsychological deficits observed in OSAS, only some of which seem to be reversible by CPAP. **d** Brain areas showing structural or functional changes in RLS. Iron deficiencies in several areas, notably the SN, may contribute to RLS, possibly via dysregulation of the closely associated dopaminergic system. These changes may in turn sensitize sensorimotor pain sensation. **e** Areas showing functional and structural abnormalities in RBD. Changes have most consistently been shown in the pons, hippocampus, and superior frontal cortex. Adapted from Desseilles et al. [5], and from illustrations by Patrick J. Lynch and C. Carl Jaffe.

(sleepwalking and RBD). We do not review sleep disorders due to disturbances from external environmental sources.

Idiopathic Insomnia

Idiopathic insomnia is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality in the neurologic control of sleep–wake regulation systems [139]. This disorder is thought to reflect an imbalance between the arousal system and the various sleep-inducing and sleep-maintaining systems. Neuroanatomic, neurophysiologic, or neurochemical dysfunctions or lesions within the sleep–wake systems are suspected in some of these patients [139].

Theoretically, either hyperactivity within the arousal system or hypoactivity within the sleep system may cause idiopathic insomnia, but hyperarousal is believed to be the final common pathway of the disorder [139]. Increased arousal might be of a physiologic, cognitive, or affective nature; it is likely that these categories overlap [6, 140], since several studies have reported increased alertness on the Multiple Sleep Latency Test, increased heart rate during the sleep period, increased anxiety on rating scales, and increased tension during wakefulness [140–142]. In addition, poor sleep leads to altered mood and motivation, decreased attention and vigilance, low levels of energy and concentration, and increased daytime fatigue [139].

Quantitative EEG recordings suggest an overall cortical hyperarousal in insomnia [143]. However, hyperarousal in primary insomnia was also found to be associated with greater increase in beta/gamma activity at sleep onset, followed by a decline of high-frequency EEG activity leading to a period of hypoarousal [143]. This could explain why some neuroimaging studies showed a cortical hyperarousal pattern in insomnia while others reported a decrease in cortical functions. In the latter case, decreased metabolism might originate from time-window coincidence of the cortical hypoarousal period to neuroimaging acquisition and therefore does not discard the hyperaousal hypothesis of primary insomnia.

Only a few studies tried to characterize the functional neuroanatomy of idiopathic insomnia disorder during sleep (referred to as primary insomnia in these reports) (Fig. 21.2a1). rCBF was estimated using ^{99m}Tc-HMPAO, a gamma-emitting radionuclide imaging agent used in the evaluation of rCBF, in five insomniacs and four normal sleepers. Patients with insomnia showed major rCBF decrease in the basal ganglia, medial frontal cortex, occipital cortex, and parietal cortex. These results suggest that idiopathic insomnia is associated with an abnormal pattern of regional brain activity during NREM sleep that particularly involves a dysfunction in the basal ganglia [144]. Four of the insomnia patients from the Smith et al. study [144] were rescanned after they had been treated with cognitive behavioral therapy [145]. After this treatment, sleep latency was reduced by at least 43 % and there was a global 24 % increase in CBF, with significant increases in the basal ganglia. Smith and collaborators proposed that such increase in brain activity might reflect the normalization of sleep homeostatic processes.

^{18}FDG PET was used to measure regional CMRglu of 7 patients with idiopathic insomnia and 20 healthy age- and gender-matched subjects during waking and NREM sleep [146]. Insomniac patients showed increased global CMRglu during sleep as compared to healthy subjects, suggesting an overall cortical hyperarousal in insomnia. Moreover, insomniac patients had a smaller decline, compared to healthy subjects, in relative CMRglu from waking to sleep states in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices (Fig. 21.3). During wakefulness, reduced relative metabolism, as compared to healthy subjects, was found in the prefrontal cortex bilaterally, in the left temporal, parietal, and occipital cortices, and in the thalamus, hypothalamus, and

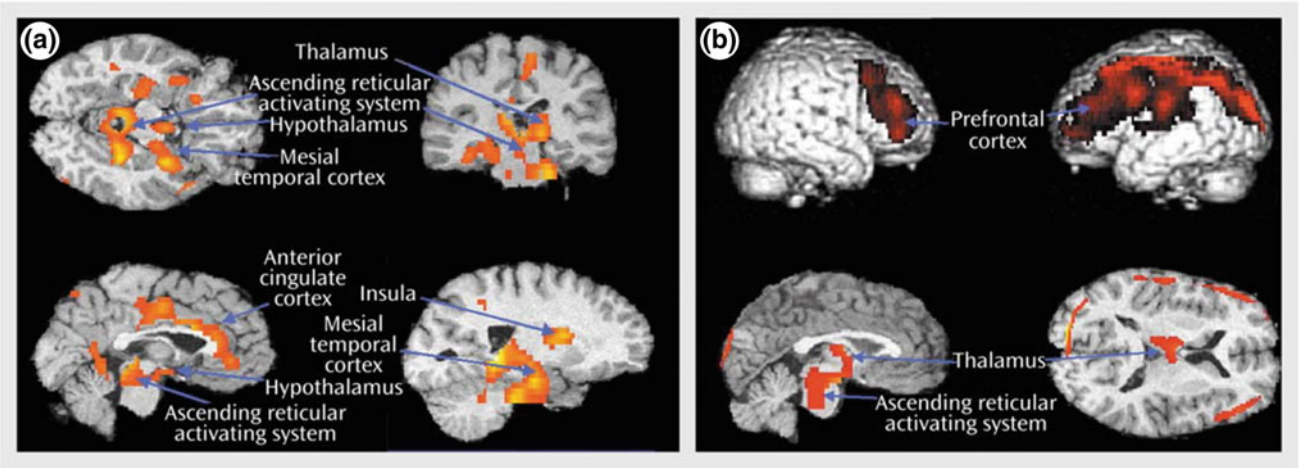

Fig. 21.3 CMRglu assessed by ^{18}FDG PET in insomniacs (versus healthy subjects) during waking and NREM sleep. **a** Brain structures that did not show decreased cerebral metabolic rate of glucose (CMRglu) from waking to sleep states in patients with idiopathic insomnia. **b** Brain structures where relative metabolism while awake was higher in healthy subjects than in patients with insomnia. Differences in all regions shown reached statistical significance ($p < 0.05$), corrected at the cluster level (Reproduced with permission from Nofzinger et al. [146]. Copyright 2004, American Psychiatric Association)

brainstem reticular formation. These findings confirm that regional brain activity does not normally progress from waking to sleep states in patients with insomnia. Additionally, it was proposed that daytime fatigue resulting from inefficient sleep may be reflected by decreased activity in the prefrontal cortex [146]. In another ^{18}FDG PET study by the same group [147] examining 15 insomniac patients, CMRglu in the pontine tegmentum and thalamo-cortical networks during NREM sleep was found to be significantly correlated with self-reported wake time after sleep onset (WASO), based on a 7-day sleep diary. Hence, elevated cortical arousal during sleep is associated with insomnia symptom severity, lending support to the hyperarousal theory of insomnia.

Additional studies have imaged idiopathic insomniacs during wakefulness, using fMRI (Fig. 21.2a1). In a first study [148], 21-year-old adult insomnia patients showed reduced medial and inferior prefrontal activation during the completion of a verbal fluency task, compared to 12 age-matched controls. In a second phase of the study after 8 weeks of non-pharmacological therapy, insomnia patients showed partial recovery of activation in these areas. These results corroborated similar findings by Nofzinger et al. [146] indicating prefrontal hypoactivation during wakefulness in insomnia. Another recent fMRI study [149] imaged 25 idiopathic insomnia patients and 25 age- and sex-matched controls during the performance of a working memory task. Interestingly, insomniacs failed both to recruit typical task-specific brain areas and to deactivate irrelevant, default-mode network regions. The authors suggested that the observed alteration in task-specific activation reflects compromised cognitive processing in insomnia, even though task performance in insomniacs was not different from controls. They attributed this to a masking effect of high perfectionism, a trait associated with insomnia.

Insomnia has been associated with high emotional reactivity [150]. An fMRI study investigated resting-state functional connectivity in the emotional system of 10 idiopathic insomnia patients and 10 matched controls [151]. Abnormalities were detected in functional connectivity between the amygdala and several cortical and subcortical areas in insomnia patients. While decreased connectivity was found for the striatum, insula, and thalamus, elevated connectivity was observed between the amygdala and the premotor cortex, sensorimotor cortex, a pathway associated with threat response. Increased motor activation is consistent with global cortical hyperarousal in insomnia.

Some recent efforts have been made to identify structural brain alterations in idiopathic insomnia, with the use of magnetic resonance imaging (MRI) (Fig. 21.2a2). While an early study found reduced hippocampal volumes in idiopathic insomnia patients compared to controls [152], subsequent studies were unable to replicate the finding [153–156]. One study found significant negative correlations between hippocampal volume and insomnia duration, as well as with a polysomnography-based index of arousal [154]. Consistent with these findings, significant inverse correlations have been reported between hippocampal volume and actigraphic WASO and sleep efficiency [153]. In one retrospective study, rostral anterior cingulate volumes were significantly greater in insomniacs [157]. The role of the anterior cingulate in insomnia is corroborated by earlier

findings in insomniacs of attenuated deactivation in this area during the transition from waking to sleep [146], and of reduced levels of inhibitory neurotransmitters in this area [158]. Additional structural studies have inspected small-scale brain modifications using VBM. VBM is a neuroimaging analysis technique that allows the investigation of focal differences in tissue composition (gray and white matter) based on high-resolution MRI scans. Prefrontal gray matter concentrations were smaller in insomniacs than in good sleepers, specifically in the orbitofrontal [156, 159] and dorsolateral prefrontal cortices [159], but these findings were not replicated in a later study [155].

Magnetic resonance spectroscopy (MRS) has been applied to the study of idiopathic insomnia. According to proton MRS (^{1}H-MRS) studies, relative concentrations of gamma-aminobutyric acid (GABA) appear to be reduced in insomniacs relative to good sleepers, globally (single-voxel) [160] and locally, in the occipital and anterior cingulate [158], although another study found occipital GABA levels to be increased instead [161]. This latter study also detected a significant inverse correlation between global GABA levels and polysomnography-based WASO. A ^{31}P-MRS study investigating gray and white matter phosphocreatine levels found this cell metabolite in lower concentrations in the gray matter of insomniac patients relative to controls, indicating a possible increase in cortical energy demand in insomnia [162].

Together, neuroimaging studies of insomnia tend to support hyperarousal theory. Diminished inhibition in the transition from waking to sleep [146], increased connectivity in the emotional and threat response systems [151], decreased ability to inhibit irrelevant cognitive processes [149], depletion of inhibitory neurotransmission [158, 160], and increased cortical energy demands [162] all are consistent with an incapacity to modulate cortical arousal across the sleep–wake cycle. In addition, evidence of reduced hippocampal volume [152], reduced prefrontal gray matter concentrations [156, 159], and increased rostral anterior cingulate volume [157] provide possible neural correlates of cognitive and emotional dysfunctions experienced in insomnia. Still, these findings require replication in larger, clinically homogeneous samples.

Narcolepsy

Narcolepsy is a disorder characterized by excessive sleepiness that is typically associated with several manifestations of so-called dissociated or isolated REM sleep features, such as muscle atonia (i.e., cataplexy), sleep paralysis, and hallucinations [139, 163]. Human narcolepsy has been found to be associated with reduction in or loss of the hypothalamic peptide hypocretin (also called orexin) implicated in arousal systems [164–167].

Anatomic Neuroimaging Studies of Narcolepsy

Structural abnormalities in narcolepsy have been examined extensively (Fig. 21.2b2). The pontine tegmentum controls transitions between sleep states and was therefore first proposed as a possible main site of anatomic or functional impairments in narcolepsy. While Plazzi and coworkers had reported pontine tegmentum abnormalities in three narcoleptic patients [167], two other structural MRI studies [168, 169] found no pontine abnormalities (except in 2 of 12 patients who had long-standing hypertension [169]. The MRI abnormalities found in Plazzi et al.'s study could reflect non-specific age-related pontine vascular changes rather than a narcolepsy-related phenomenon [167].

VBM has been employed to find evidence for hypothalamic abnormalities in narcoleptic patients, reporting equivocal results. An early study found no structural change in brains of patients with hypocretin-deficient narcolepsy [170]. Subsequent studies did find cortical gray matter reduction predominantly in frontal brain regions [171–174], as well as in inferior temporal regions [175]. Interestingly, relative global gray matter loss was independent of disease duration or medication history, and there were no significant subcortical gray matter alterations [175]. Significant gray matter concentration decreases were found in the hypothalamus, cerebellum (vermis), superior temporal gyrus, and right nucleus accumbens in 29 narcoleptic patients relative to unaffected healthy controls [176] (Fig. 21.4). Given the widespread projection sites of hypocretin, the decreases in gray matter could thus reflect secondary neuronal losses due to the destruction of specific hypocretin projections. The results of this study were later corroborated by two other VBM studies [171, 177]. More recent MRI studies in narcolepsy with cataplexy identified volumetric decreases in the bilateral hippocampus [178] and amygdala [179]. Notably, amygdalar deficits may underlie emotional dysregulation in narcolepsy.

Anatomic alterations have also been described using MRI cortical thickness measurements. A localized thinning of the cortex was detected in the prefrontal, cingulate, inferior parietal, and temporal areas in narcoleptic-cataplectic individuals [180]. Another study measured increased cortical volume and thickness in the dorsolateral prefrontal cortex of narcoleptic patients [181]. Furthermore, early-onset narcoleptic patients exhibited thinner cortex than late-onset narcoleptics in the precentral gyrus, inferior parietal cortex, and temporal regions. These results were interpreted as reflecting distinct pathological subtypes [181].

Recent studies have used DTI to detect alterations in fiber tract integrity, based on water diffusion in the brain. Using FA and mean diffusivity measures, it was shown that white matter tracts were disrupted in frontal, temporal, and anterior cingulate regions in narcolepsy [173]. Another DTI study found similar results, in addition to white matter

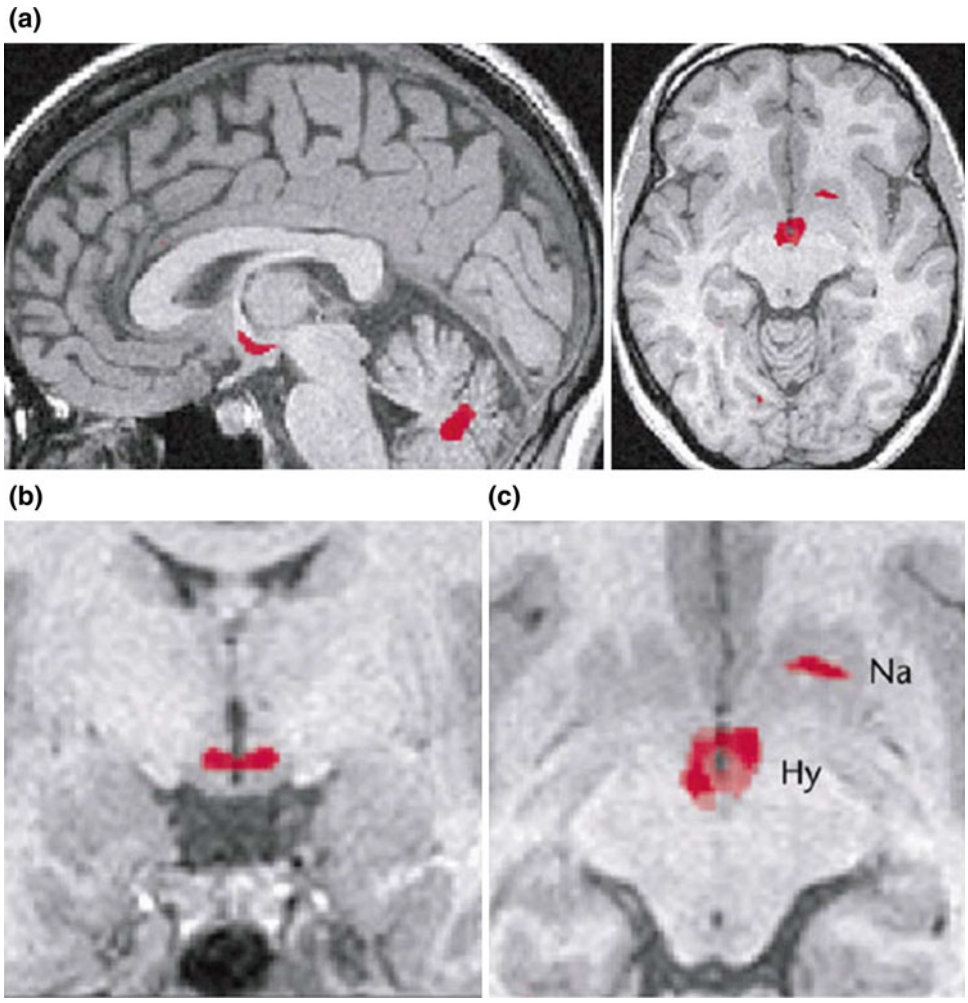

Fig. 21.4 Statistical parametric maps demonstrating the structural difference in *gray* matter between narcolepsy patients and healthy control subjects. Differences are shown superimposed in *red* on a normalized image of a healthy control subject. The *left panel* in A is the *left side* of the brain. A significant decrease in *gray* matter concentration was found in the hypothalamus (Hy) (**a**–**c**) and in the area of the *right* nucleus accumbens (Na) (**a** and **c**) (Reproduced with permission from Draganski et al. [176]. Copyright 2002, Nature Publishing Group)

abnormalities in the pons, right hypothalamus and left mesencephalon, consistent with a dysfunction in the hypothalamic hypocretin system in narcolepsy [182].

Proton MRS was also used to assess the *N*-acetylaspartate (NAA) and creatinine plus phosphocreatinine (Cr + PCr) content in specific brain areas of narcoleptic patients. A reduced NAA/Cr + PCr ratio indicates reduced neuronal function, which could reflect neuronal loss (i.e., fewer neurons) but could also be due to reduced activity of existing neurons. An analysis of spectral peak area ratios revealed a decrease in the NAA/Cr + PCr ratio in the hypothalamus [183] and the ventral pontine areas [184] of narcoleptic patients compared with control subjects. These results may indicate structural damage to these areas in narcolepsy.

Several factors can explain equivocal results across structural neuroimaging studies, such as inhomogeneous patient groups, history of treatment, or, for VBM, prestatistical image processing and limited sensitivity of this technique. VBM studies with larger samples of drug-naive patients are required to identify reliable structural abnormalities in narcolepsy.

Functional Neuroimaging Studies of Narcolepsy

A number of studies have examined brain metabolic differences in narcoleptic patients in the waking state (Fig. 21.2 b1). Early functional observations using ^{133}Xe inhalation showed that, during wakefulness, CBF in the brainstem was lower in narcoleptic patients than in normal subjects. However, after sleep onset (3 of 13 cases in REM sleep), the CBF increased in all regions, particularly in temporoparietal regions. This pattern was supposedly attributed to dreaming activity, in line with prior reports showing increased regional blood flow in temporoparietal areas during visual dreaming and hypnagogic hallucinations [185, 186].

A ^{99m}Tc-HMPAO SPECT study in six narcoleptic patients found similar HMPAO uptake in the waking state and REM sleep [187], suggesting a similar overall cortical activity. Data analysis using regions of interest additionally indicated an activation of parietal regions during REM sleep [187]. The latter result is intriguing given the parietal deactivation usually observed by PET studies during normal REM sleep [8]. Further studies during REM sleep are needed to confirm these results in a larger population.

Two ^{18}FDG PET studies were conducted in the waking state to examine differences in narcoleptic brain activation. In the first study, a sample of 24 narcoleptic patients had reduced CMRglu in the bilateral posterior hypothalami, mediodorsal thalamic nuclei, and frontal and parietal cortices, compared to controls [188]. The second study instead found a CMRglu increase in the cingulate and visual association cortices in 21 narcoleptic patients also suffering from cataplexy [189]. A SPECT study revealed hypoperfusion during wakefulness in several areas including the bilateral anterior hypothalami, caudate nuclei, pulvinar, parahippocampal gyri, cingulate gyri, and prefrontal cortices [190].

There are very few data describing the neural correlates of cataplexy in narcoleptic patients (Fig. 21.2b1). One SPECT study was conducted on two patients during a cataplexy episode compared to REM sleep or a baseline waking period [191]. During cataplexy, perfusion increased in limbic areas (including the amygdala) and the basal ganglia, thalami, premotor cortices, sensorimotor cortices, and brain stem, whereas perfusion decreased in the prefrontal cortex and occipital lobe. Increased cingulate and amygdala activity may relate to concomitant emotional processing that is usually reported as a powerful trigger of cataplexy. However, such hyperperfusion in the pons, thalami, and amygdaloid complexes was not found in two subsequent studies [189, 192]. A more recent PET study imaged two patients during a cataplectic attack and found a large decrease in glucose metabolism in the hypothalamus, as well as increased metabolism in pre-postcentral gyri and somatosensory cortex [189].

Based on the clinical observation that cataplexy episodes are often triggered by positive emotions (e.g., hearing or telling jokes), an fMRI study was performed on narcoleptic patients and controls while they watched sequences of humorous pictures [193]. Group comparisons revealed that humorous pictures elicited reduced hypothalamic response together with enhanced amygdala response in the narcoleptic patients. These results suggest that hypothalamic hypocretin activity physiologically modulates the processing of emotional inputs within the amygdala and that suprapontine mechanisms of cataplexy might involve a dysfunction of hypothalamic–amygdala interactions triggered by positive emotions [193, 194]. Another fMRI study examined amygdalar response to emotional stimuli, by pairing visual stimuli with painful electric shock. Whereas healthy controls showed enhancement of amygdalar response to conditioned aversive stimuli, no such enhancement was observed in narcoleptic subjects [195]. In addition to this abnormal emotional circuitry, abnormal reward circuitry was evident in another report by the same group [196].

Neurotransmission in Narcolepsy

Given the role of acetylcholine as an important neurotransmitter in the generation of REM sleep [28, 197], it was hypothesized that disturbances in the cholinergic system might underlie narcolepsy. However, a PET study with ^{11}C-*N*-methyl-4-piperidylbenzilate found no evidence for a change in muscarinic cholinergic receptors in narcoleptic patients [198].

Likewise, the dopamine system has been probed by PET and SPECT in narcoleptic patients because increased dopamine D_2 receptor binding was shown in the brains of deceased narcoleptic patients [199, 200]. The results from these neuroimaging studies remain mostly inconsistent. One SPECT study showed elevated D_2 receptor binding in the striatal dopaminergic system, correlating with the frequency of cataplectic and sleep attacks in seven patients with narcolepsy [201]. However, other PET [202–204] or SPECT [205, 206] ligand studies did not find such change in D_2 receptor binding. A potential explanation for this discrepancy might be related to the drug treatment of narcoleptic patients. Indeed, considerable increase in the uptake of ^{11}C-raclopride, a specific D_2 receptor ligand, was observed in the putamens of narcoleptic subjects older than 31 years who underwent various regimens of prolonged treatment [207]. Likewise, despite the fact that the binding of iodobenzamide (IBZM, a highly selective CNS dopamine D_2 receptor ligand), was similar in narcoleptic patients and normal controls, treatment by stimulants and/or antidepressants for 3 months significantly changed ligand uptake in four of five patients [206]. Therefore, elevated postmortem dopamine binding might be due to the long-term effect of prior treatment rather than intrinsic modifications.

Brain Response to Drug Probe in Narcolepsy

The effects of stimulant drugs on cerebral function in narcoleptic patients were assessed using functional imaging. The effect of amphetamines was evaluated using fMRI in two patients with narcoleptic syndrome [208]. The extent of the brain response to auditory and visual stimulation decreased after amphetamine administration in normal subjects. The reverse pattern was observed in the narcoleptic patients. These findings remain difficult to interpret, and larger samples of patients should be studied.

Modafinil is a wakefulness-promoting psychostimulant used to treat narcoleptic patients. Two fMRI studies have evaluated its effect on brain perfusion responses. A first study found that normal subjects showed larger brain responses to a multiplexed visual and auditory stimulation paradigm at 10:00 A.M. than at 3:00 P.M. in visual areas, but not in auditory areas, suggesting time-of-day influences [209]. Surprisingly, the reverse pattern of activity was

observed in a group of 12 narcoleptic patients, with greater perfusion at 3:00 P.M. than 10:00 A.M.. Critically, modafinil administration did not modify the average level of activity either in normal subjects or in narcoleptics ($n = 8$), but post-drug activity level was inversely proportional to the predrug activity level. These findings are not easy to interpret but might suggest that modafinil can modulate brain activation in response to external stimuli. The second fMRI study tested the effect of modafinil on brain activation during a working memory task in healthy subjects, following a night of sleep deprivation. Modafinil at once improved working memory performance and enhanced activation in the executive network, specifically in the prefrontal and anterior cingulate cortices [210].

The metabolic effect of modafinil was studied in healthy individuals using ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) SPECT before and after the administration of the stimulant or a placebo [211]. Modafinil increased wakefulness and rCBF to areas in the brain associated with arousal, emotions and executive function, including the prefrontal, insular, cingulate, middle/inferior temporal and parahippocampal cortices and the pons. An ^{18}FDG PET study imaged baseline CMRglu in awake patients and controls before and after treatment with modafinil. Decreased CMRglu was observed in the brainstem, hypothalamus, thalamus, and mesio-temporal areas in narcoleptics compared to controls. When comparing pre- and post-treatment conditions in narcoleptic patients, an increase in CMRglu was found in the left hippocampus post-modafinil [212]. A second ^{18}FDG PET study compared CMRglu levels in 14 narcolepsy-cataplexy patients treated with psychostimulants and anticataplectics, and 7 narcolepsy-cataplexy patients that were not treated with drugs. Treated narcoleptic had higher levels of CMRglu in their cerebellum and primary sensory motor cortex. However, these results were hard to interpret due to sample heterogeneity [189].

Summary

Structural and functional neuroimaging studies in narcolepsy with cataplexy show remarkable convergence. Primarily, the hypothalamus displays consistent abnormalities in narcoleptic patients, both structural and functional. Hypothalamic involvement in narcoleptic psychopathology is consistent with the characteristic loss of hypocretinergic neurons in this disorder. The limbic system also shows abnormal responding, including the amygdala, which may reflect emotional dysregulation seen in the disorder and triggering cataplectic episodes. Structural abnormalities were equally found in the hippocampus and various cortical areas, perhaps underlying dysfunctions in cognitive processing. Sparse imaging data acquired during cataplexy itself suggest a possible role of the hypothalamus and somatosensory cortex. As for treatment response, modafinil seems to alter metabolism in a variety of areas, but none have stood out from the few studies to date. Despite recent breakthroughs in the pathophysiology of narcolepsy, more studies using state-of-the-art technology of acquisition and analysis of functional neuroimaging data are needed to better characterize the functional organization of the narcoleptic brain during wakefulness and sleep.

Recurrent Hypersomnia

Recurrent hypersomnia is a disorder characterized by recurrent episodes of hypersomnia that typically occur weeks or months apart [139]. One SPECT study in a 24-year-old male with recurrent hypersomnia showed decreased blood flow in the left thalamus during the hypersomnolent period, but failed to report any abnormal activation during recovery or remission periods [213]. This case report neuroimaging study provides only limited information about possible pathophysiologic mechanisms of this disorder. By contrast, other clinical and electrophysiologic studies clearly point toward a hypothalamic rather than a thalamic dysfunction [214, 215].

A typical form of recurrent hypersomnia, KLS, is characterized by periodic hypersomnia as well as behavioral and cognitive abnormalities, mainly in male adolescents [216]. Neuroimaging studies of KLS patients have revealed normal brain anatomy [216–218]; however, functional abnormalities were observed in SPECT. In an early SPECT study with ^{99m}Tc-ECD, unilateral hypoperfusion of both thalami was found in a sample of 27 KLS patients. These hypoperfusions consistently occurred during the symptomatic period [218] and were confirmed in later studies using both SPECT and ^{1}H-MRS [219–221]. During asymptomatic periods, perfusion of thalami returned to normal levels in all subjects, while other abnormalities in hypoperfusion persisted, mainly in the temporal lobe [218]. Other studies corroborated that hypoperfusion of the temporal lobe persists in asymptomatic patients [220]. Hypoperfusion of both thalami and basal ganglia [217, 220], as well as the frontal [222–224] and temporal lobe [216, 218, 220, 222, 225, 226], may provide insight to the pathophysiology of KLS, but the roles of the brain structures are not yet clear.

Obstructive Sleep Apnea Syndrome (OSAS)

OSAS is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation [139]. Population-based epidemiologic studies have revealed a high prevalence (1–5 % of adult men) of OSAS. They also associate OSAS with significant morbidity, such as hypertension, cardiovascular disease, stroke, and motor vehicle accidents [227]. OSAS may lead to functional and structural brain alterations. Functional alterations such as sleep

fragmentation are often associated with neuropsychological deficits that can be reversible after treatment of OSAS. Structural alterations may indicate irreversible consequences on brain integrity and suggest permanent cognitive impairment, although this proposal remains a matter of debate in the literature, especially given recent structural imaging data showing a reversibility after treatment [228].

The pathophysiology of OSAS is complex and not yet completely understood. Several studies suggest that OSAS across all age groups is due to a combination of both anatomic airway narrowing and abnormal upper airway neuromotor tone. Notwithstanding the known anatomic factors, such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy, that contribute to OSAS, clear anatomic contributing factors cannot always be identified [139]. This suggests that alterations in upper airway neuromuscular tone also play an important role in the etiology of OSAS [229]. The pathophysiology of OSAS also includes enhanced chemoreflex sensitivity and an exaggerated sympathetic response during hypoxemic episodes [230].

Apnea episodes in OSAS patients have considerable hemodynamic consequences, which are mediated by a complex cascade of physiologic events. Repetitive episodes of apnea trigger marked fluctuations in both blood pressure and heart rate, with consequent effects on the estimates of cardiovascular variability [6]. Several important regulatory mechanisms in cardiovascular homeostasis seem to be impaired in OSAS patients. Specific chemoreceptors seem to be implicated in the pathophysiology of OSAS [231]. For instance, the ventilatory response to carbon dioxide is elevated in OSAS patients [231] due to an elevation of the partial pressure of carbon dioxide that delimits carbon dioxide ventilatory recruitment threshold. An altered autonomic balance has been suggested as one possible pathogenic factor. This autonomic dysfunction has been thought to be implicated in the subsequent development of cardiovascular diseases in patients with OSAS.

Functional Neuroimaging Studies of OSAS

Several fMRI studies have been conducted in OSAS patients to characterize the neural correlates of integrated afferent airway signals with autonomic outflow and airway motor response [232–234]. For instance, altered response after a Valsalva maneuver involves cerebellar, limbic, and motor area deactivation. Enhanced sympathetic outflow after a forehead cold pressor challenge results in both diminished response in the thalamus, hippocampus, and insula, and exaggerated response in the cingulate cortex, cerebellum, and frontal cortex. Mandibular advancement led to decreased fMRI response in the left cingulate gyrus and the bilateral prefrontal cortices in 12 healthy subjects during induced respiratory stress [235]. Simultaneously, the subjective effects of this treatment were assessed by a visual analog scale that confirmed successful reduction of respiratory stress.

OSAS has been associated with distinctive cognitive alterations in various domains. Both hypoxemia and fragmented sleep are proposed as the main factor leading to neurocognitive impairments during wakefulness [236–243]. Several studies emphasized the deterioration of executive functions in OSAS patients, including the inability to initiate new mental processes [244, 245] and deficits in working memory [244, 246], analysis and synthesis [244, 246], contextual memory [247], selective attention [248], and continuous attention [248]. A meta-analysis showed that untreated patients with OSAS had a negligible impairment of intellectual and verbal functioning but a substantial impairment of vigilance and executive functioning [249].

A number of functional imaging studies of OSAS patients have used fMRI to evaluate BOLD contrasts during performance on cognitive tasks (Fig. 21.2c1). Generally, these studies have found deactivations in various regions [250–254], while some instead showed increases in activation [255] or mixed results [252, 256, 257]. For example, Ayalon et al. [253] compared 14 OSAS patients with 14 healthy controls on a sustained attention task and found task-related reductions in activation in OSAS patients across parietal, cingulate, and frontal regions typically recruited in attention tasks. Archbold et al. [256] found that OSAS severity correlated with increased activation of the right parietal lobe during a working memory task, in a sample of 9 treatment-naïve male OSAS patients. Deactivations are consistent with OSAS-related structural deterioration (described below), whereas activation increases may represent compensatory recruitment. More recent studies have focused on resting-state functional connectivity changes and have found regional reductions in connectivity in the medial and dorsolateral prefrontal cortices, which make up part of the default-mode network [258, 259]. Concordantly, default-mode network deactivation was compromised in OSAS patients during a visuospatial N-back task, in parallel with performance deficits [252, 260].

Aside from fMRI studies during cognitive performance, functional correlates of OSAS have also been studied during restful wakefulness, using PET and SPECT. A ^{99m}Tc-ECD SPECT study observed decreased baseline rCBF in the parahippocampal and lingual gyri of OSAS patients compared to healthy volunteers [261]. Using ^{18}FDG PET, another group found reduced CMRglu in the prefrontal, parieto-occipital, and cingulate gyri of OSAS patients, compared to healthy controls [262].

Long-term consequences of OSAS have been rarely assessed after nasal continuous positive airway pressure (CPAP) treatment. An early ^{99m}Tc-HMPAO SPECT study in 14 adult OSAS patients reported a marked frontal hyperperfusion in 5 patients [263]. In contrast, regional analysis showed reduced perfusion in the left parietal region. All these changes were reversed by effective CPAP therapy, suggesting that the main deleterious effects of OSAS on

brain activity are reversible. According to the authors, there might be an apnea-associated effect of local vascular autoregulation mechanisms acting to compensate systemic blood flow alterations or blood gas changes in OSAS. Similar findings were obtained in an fMRI study, where hyperactivation of prefrontal and hippocampal areas was reversed with 3 months of CPAP treatment [257]. In a recent study, 2 months of CPAP treatment improved task-related default-mode network deactivation, concomitantly with improvements in behavioral performance [260].

Anatomic Neuroimaging Studies of OSAS

Structural modifications of brain morphology in OSAS have been studied extensively in several modalities (Fig. 21.2c2). In an early study, structural changes were assessed using VBM in 21 patients with OSAS and in 21 control subjects [264]. Gray matter loss was apparent in patients with OSAS in multiple brain sites involved in motor regulation of the upper airway as well as in various cognitive functions, including the frontal and parietal cortices, temporal lobes, anterior cingulate, hippocampus, and cerebellum. Additional VBM studies found gray matter loss in similar regions, mainly in the prefrontal, anterior cingulate, parietal, and hippocampus [228, 258, 262, 265, 266, 267, 268]. These anatomic changes were often [228, 266, 267] but not always [262] associated with cognitive deficits, notably memory impairment. Female gender [269] and depressive symptoms [270] were associated with exacerbated neural damage and neurocognitive symptoms from OSAS. Another MRI study compared both neuroanatomical and neuropsychological effects of hypoxia in patients with either carbon monoxide poisoning or OSAS and found a hippocampal atrophy in both groups [266]. Of note, a linear relationship between hippocampal volume and memory performance selectively in the OSAS group was found for a subset of tests (the delayed recall or the Rey-Osterrieth Complex Figure Design and Trail 6 of the Rey Auditory Verbal Learning Test among others). Moreover, hippocampal volume was related to performance on nonverbal information processing (Wechsler Adult Intelligence Scale–Revised Block Design) in both groups. In a more recent study, hippocampal volume was also negatively correlated with excessive daytime sleepiness [268]. Further investigation will be necessary to better delineate the specificity and contribution of hippocampal atrophy in OSAS. A set of interesting correlations between indices of OSAS severity and prefrontal cortex changes were observed with MRI. Apnea–hypopnea index was negatively correlated with frontal gray matter volumes [228]. Also in the frontal regions, prolonged arterial oxygen desaturation correlated with gray matter decreases [228], deactivations during working memory tasks [251, 252], and decreased cortical connectivity [259]. In one of these studies, 3 months of CPAP treatment in 17 treatment-naïve OSAS patients resulted in the recovery of gray matter concentrations in the hippocampus and frontal regions, alongside significant improvements in neurocognitive performance [228]. These findings underline the effectiveness of CPAP treatment in both physiologic and cognitive recovery from OSAS-related neural damage.

Single-voxel ^{1}H-MRS has also been used to assess whether OSAS can induce axonal loss or dysfunction, or myelin metabolism impairment. An early study using this technique showed that the NAA/Cr ratio in cerebral white matter was significantly lower in patients with moderate to severe OSAS than in patients with mild OSAS and healthy subjects [271]. A series of studies followed which compared OSAS patients to controls and found significantly lower NAA/Cr [272, 273], NAA/choline (Cho) [273, 274], and Cho/Cr [275] ratios in frontal white matter, as well as greater Cho/Cr ratios in the thalamus [273] and temporal regions [272]. In addition, apnea–hypopnea index was negatively correlated with NAA/Cr ratios [272]. These findings may explain some of the deficits in executive function associated with OSAS. Consistent with the VBM results noted previously, decreases in absolute and relative creatine-containing compounds in the left hippocampal area correlated with increased OSAS severity [274, 276, 277, 278] and worse neurocognitive performance [277]. Together, VBM and spectroscopy studies point to an atrophy and/or dysfunction of hippocampal regions in OSAS. In a ^{1}H-MRS study of the effects of CPAP on OSAS severity, NAA in the parieto-occipital cortex was significantly lower in 14 OSAS patients than in controls, but this reduction persisted after CPAP therapy despite clinical, neuropsychological, and neurophysiologic normalization [279]. Accordingly, a later MRS study found no significant differences in creatine-containing compounds after 6 months of CPAP treatment [274].

Summary

Altogether, these findings suggest that neuropsychological deficits in OSAS might relate to various alterations in the prefrontal cortex, hippocampus, and parietal cortex. In particular, volumetric decreases may provide a useful biomarker of OSAS severity [280]. Reduced functional connectivity of the default-mode network may also relate to cognitive deficits in OSAS. Even if abnormal brain activations and even structural changes seem reversible under CPAP, several studies have suggested that not all neuropsychological impairments disappear after the treatment [245, 281, 282]. Although the basic pathophysiologic mechanisms of OSAS are not completely understood, a dysregulation in autonomic control seems to play an important role [232–234].

Restless Legs Syndrome and Periodic Limb Movements

Periodic limb movements (PLM) during sleep and restless legs syndrome (RLS) are distinct but overlapping disorders. RLS is typified by an irresistible urge to move the legs (and less often, the arms), especially during sleep onset. The compulsion is associated with relentless feelings of discomfort from deep inside the limbs [283, 284]. PLM is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep [284]. While these movements disturbed sleep and can result in awakening, patients are mostly unaware of the movements or even that their sleep has been disturbed. Diagnosis requires a polysomnographic recording along with a complaint such as "unrefreshing" sleep [284, 285].

RLS and PLM commonly co-occur. However, PLM is non-specific, occurring in isolation in healthy individuals or comorbid with other sleep disorders such as narcolepsy, RBD, and sleep apnea [285]. Given their close association, few neuroimaging studies have investigated PLM alone and instead RLS and PLM are most often considered in concert. The present section will first cover neuroimaging studies focused on RLS (Fig. 21.2d) and will end by covering the few studies of PLM alone.

Restless Legs Syndrome

An early ^{18}FDG PET study found no differences in glucose metabolism between six RLS patients and six age-matched controls, albeit when measured outside the symptomatic period [286]. An fMRI study also attempted to localize some cerebral generators of leg discomfort and PLM in RLS [287]. During RLS leg discomfort, the study showed a bilateral activation of the cerebellum and contralateral activation of the thalamus in patients. A later fMRI study examined brain activation in concert with electromyography measures of tonic activity in the legs, in 7 RLS patients [288]. Tonic activity was inversely correlated with reported discomfort in the legs and with cerebellar activation and positively correlated with activation in the sensorimotor cortex, cingulate gyrus, precuneus, and occipital cortex.

An inhibition of descending inhibitory pathways implicating dopaminergic, adrenergic, and opiate systems is thought to be involved in RLS pathogenesis [289]. Patients' condition worsens when dopamine antagonists are given [290], whereas dopaminergic drugs have been shown to relieve RLS [291–293].

Dopamine research in RLS has centered mainly on the striatum, probing both presynaptic DAT and postsynaptic D_2 receptor occupancy. Striatal DAT can be taken as a measure of dopaminergic neuron density in the substantia nigra (SN). Some PET studies found reduced presynaptic dopamine activity in the striatum of RLS patients compared to controls, using either ^{11}C-methylphenidate [294] or ^{18}F-dopa [295, 296], although an early study using ^{18}F-dopa found no such difference in a small sample [297]. Additionally, some SPECT studies found no change in DAT in RLS compared to controls, using ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-β-CIT) [298, 299] or ^{123}I-N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β -(4-chlorophenyl) tropane (^{123}I-IPT) [300, 301]. Variable pharmacokinetic properties of radioligands may contribute to explain the discrepancy in these findings. DAT binding seems independent of clinical severity and time of day [294]. An additional SPECT study employed SPECT with ^{123}I-β-CIT and ^{123}I-IBZM, and contrarily to previous presynaptic dopamine studies, DAT density showed an increase in the striatum, as well as the caudate and posterior putamen [302]. The authors concluded that DAT dysregulation may be responsible for RLS pathogenesis, rather than DAT upregulation or downregulation specifically.

Results of postsynaptic D_2 receptor binding studies are also ambivalent. Among SPECT studies using ^{123}I-IBZM, some found no difference [300, 303, 304], and others detected a reduction in striatal D_2 receptor binding in RLS patients compared to controls [298, 305, 306, 307, 308]. In one of these studies, treating patients with dopamine replacement therapy increased the IBZM binding and improved sleep quality in these patients [305]. Two PET studies with ^{11}C-raclopride found conflicting results, with one showing an increase [295] and the other a decrease [309] in striatal D_2 receptor binding. Different pharmacological histories may explain this discrepancy; only the latter study used drug-naïve patients. Indeed, it has been shown that chronic drug treatment can downregulate D_2 receptors, thus decreasing ligand binding [310]. Another study using ^{11}C-FLB457 found increased binding potential in the striatum as well as in the insula, thalamus, and anterior cingulate cortex, all of which are components of the medial nociceptive system [309]. Upregulation of D_2 receptors in this area may be the consequence of endogenous dopamine depletion. Similar to presynaptic dopamine findings, clinical severity, and time of day had no effect on D_2 binding potential. [309]. A recent PET study using ^{11}C-raclopride found that RLS patients had reduced D_2 receptor binding potential in the putamen and caudate but not ventral striatum [311]. Altogether, pre- and postsynaptic dopamine studies remain inconclusive.

The role of dopamine in RLS pathophysiology may be better understood by taking into account studies implicating the cerebral metabolism of iron [312] (Fig. 21.2d). Iron and the dopaminergic system are linked since iron is an important cofactor for tyrosine hydroxylase, the step-limiting enzyme in dopamine synthesis, and also plays a major role

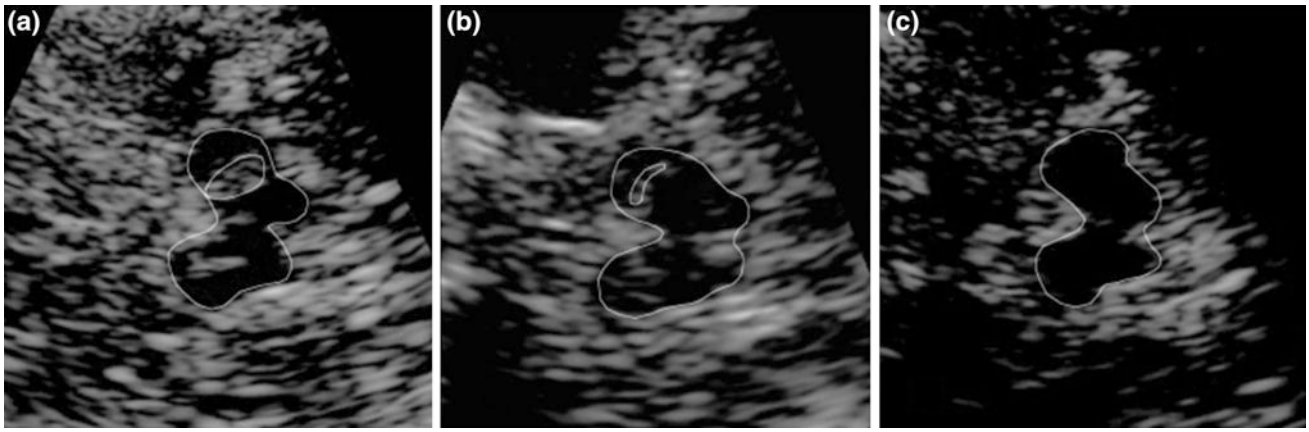

Fig. 21.5 Transcranial ultrasound images (axial plane) in three patients. **a** Patient with Parkinson's disease (PD). **b** Control subject. **c** Patient with restless legs syndrome (RLS). Midbrain is *encircled* and areas of hyperechogenicity are *encircled* in (**a**) and (**b**). There is a progression of decreased echogenicity from PD to healthy control to RLS (Reproduced with permission from Schmidauer et al. [319]. Copyright 2005, American Neurological Association)

in the functioning of postsynaptic D_2 receptors [6]. Notably, increased iron concentrations in the midbrain are a reliable biomarker in PD [313, 314]. Consistent with a link between the dopaminergic system and iron, Allen et al. [315] found decreased regional iron concentrations in the SN and putamens of five patients with RLS, both in proportion to RLS severity. In addition, Earley et al. [316] found diminished iron concentration across 10 brain regions in early-onset RLS patients but not in late-onset RLS patients when compared to controls. Transcranial ultrasound has also been used to measure decreased iron levels in the SN, capitalizing on iron's echogenic effect [317–319]. Of note, midbrain iron concentrations in RLS patients were significantly reduced relative to control subjects and showed an even more pronounced reduction relative to PD patients (Fig. 21.5) [319]. Iron depletion was also found in other areas than the SN, such as the thalamus and caudate, suggesting RLS is a multiregional disorder [317].

Opioid receptor agonists improve RLS symptoms [320], consistent with RLS as a disorder of the nociceptive system. This effect may be mediated by dopamine and may not necessarily reflect a endogenous opioids deficiency [321]. In support of this, one PET study examined opioids in RLS, using ^{11}C-diprenorphine (a non-selective opioid receptor ligand), and found no differences between patients and controls, although some correlations were detected between RLS severity or pain scores and decreased opioid binding in several brain areas [322]. These decreases in opioid receptor availability likely result from the endogenous release of opioids in response to RLS-related pain and discomfort.

Structural cerebral abnormalities have been reported in patients with idiopathic RLS [323]. High-resolution T1-weighted MRI of 51 patients and 51 controls analyzed using VBM revealed a bilateral gray matter increase in the pulvinar in patients with idiopathic RLS. These authors suggest that changes in thalamic structures are either involved in the pathogenesis of RLS or may reflect a consequence of chronic increase in afferent input of behaviorally relevant information. A number of VBM and DTI studies followed. Two studies by a same research group found gray matter decreases in the primary sensorimotor cortex using VBM (63 RLS patients, 40 controls) [324] and white matter alterations near this area and near the thalamus, using DTI (45 patients, 30 controls) [325]. These changes may, however, have been due to patient pharmacological treatment history. Indeed, four subsequent studies examining unmedicated patients detected no neuroanatomical differences using VBM [326–329] and DTI [329], except for a slight gray matter increase in the orbitofrontal gyrus and hippocampus [328]. However, these studies had possessed lower power due to smaller samples (from 15 to 20 patients). A recent multimodal study using ^{1}H-MRS found a significant reduction of *N*-acetylaspartate concentration and *N*-acetylaspartate to creatine ratio in the medial thalamus in RLS patients versus controls [330]. These results lend support to a role of thalamic dysfunction in RLS pathophysiology, although concurrent fMRI and DTI in this same study did not reveal thalamic alterations. It remains unclear whether RLS is associated with any consistent neuroanatomical changes.

A recent ^{1}H-MRS study demonstrated that thalamic glutamate/glutamine (Glx)/Cr levels were augmented in RLS patients, with respect to controls [331]. Furthermore, correlations were observed between Glx/Cr and WASO, a sleep variable related to RLS, but no correlation was found with PLM rate. This is interesting given that dopamine, to the contrary, has been correlated strongly with PLMs and not with WASO. The authors propose two dichotomous systems involved in RLS pathology, namely a glutamatergic arousal system and a dopaminergic motor system. Hence, the

glutamatergic system may be an important target for further pathophysiologic studies of RLS.

Periodic Limb Movements

A few studies have focused specifically on PLM. An fMRI study combining PLM and sensory leg discomfort showed activity in the cerebellum and thalamus with additional activation in the red nuclei and brainstem close to the reticular formation [287]. Notably, when subjects were asked to voluntarily imitate PLM, there was no activation in the brainstem, but rather additional activation in the globus pallidus and motor cortex. These results suggest an involuntary mechanism of induction and a subcortical origin for PLM.

Dopaminergic transmission has been studied in relation to PLM. Presynaptic dopamine transmission was measured in 11 patients with PD using SPECT with ^{123}I-β-CIT [308]. Patients with PD showed a large decrease in striatal binding relative to controls, as predicted. A negative correlation was detected between the number of polysomnography-based PLMs and striatal dopamine binding values. This indicates a potential role of presynaptic dopamine deficiency in PD-induced PLM. A few studies found reduced D_2 receptor occupancy in the striatum of PLM patients using SPECT and ^{123}I-IBZM [306, 307]. Dopamine replacement therapy can reverse this pattern and restore sleep quality [305].

Summary

Studies on RLS seem to indicate iron depletion in several brain regions, especially in the SN, which may interact with dopamine metabolism to unbalance the sensorimotor control of pain. Functional studies on opioids and glutamate are few, but may shed further light on the disorder. Meanwhile, structural studies have not revealed any consistent changes in brain structure in RLS. The thalamus stands out as a potentially important area in RLS pathology, having shown functional and structural abnormalities. Further research into RLS and PLM brain activation during sleep is needed to better understand these disorders.

Sleepwalking

Sleepwalking, also known as somnambulism, is an arousal parasomnia consisting of a series of complex behaviors that result in large movements during sleep [332]. It is perceived as a dissociation state whereby most of the brain exhibits non-REM sleep patterns, except motor-related areas. One

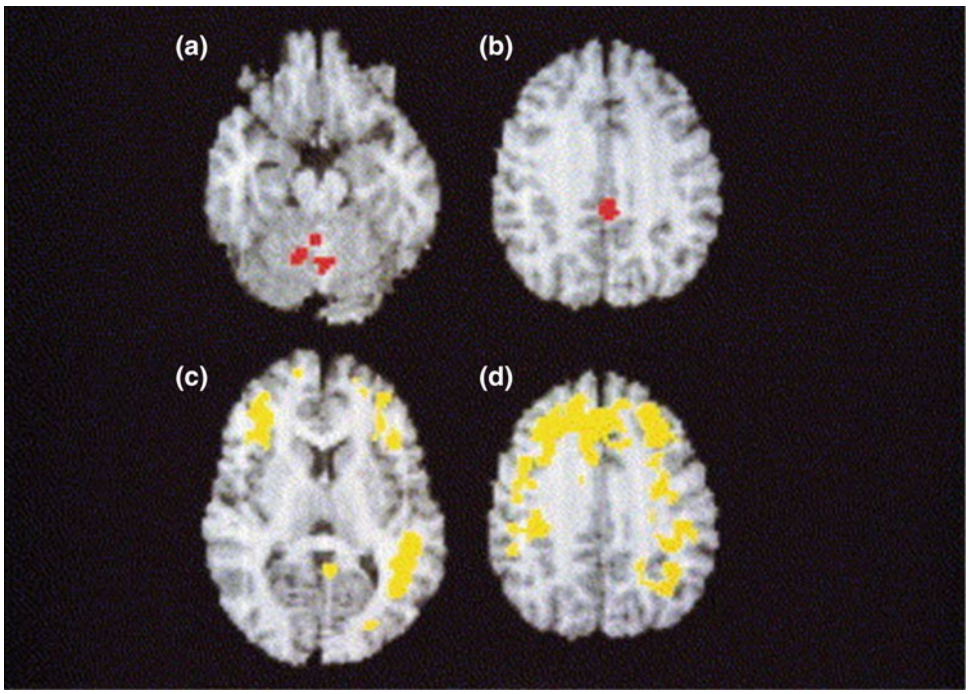

Fig. 21.6 SPECT findings during sleepwalking after integration into the appropriate anatomic magnetic resonance image. The highest increases of regional CBF (>25 %) during sleepwalking compared with quiet stage 3–4 NREM sleep are found in the anterior cerebellum (i.e., vermis) (**a**), and in the posterior cingulate cortex (**b**). However, as compared to data from normal volunteers during wakefulness, large areas of frontal and parietal association cortices remain deactivated during sleepwalking, as shown in the corresponding parametric maps. Note the inclusion of the dorsolateral prefrontal cortex (**c**), mesial frontal cortex (**d**), and left angular gyrus (**e**) within these areas (Reproduced with permission from Bassetti et al. [333]. Copyright 2000, The Lancet)

16-year-old male subject was studied during sleepwalking using ^{99m}Tc-ECD SPECT [333]. Compared to awake normal volunteers (n = 24), a decrease in rCBF in the frontoparietal associative cortices was found. Additionally, the posterior cingulate cortex showed increased rCBF during the sleepwalking episode, with respect to the patient's baseline activity. These results suggest that this state dissociation arose from combined activation of thalamo-cingulate pathways and persisting deactivation of other thalamo-cortical arousal systems (Fig. 21.6). Since only one patient has ever been studied while sleepwalking, further studies with larger sample sizes are needed to confirm these findings.

REM Sleep Behavior Disorder

This condition, initially described by Schenck et al. [334], is characterized by brisk movements of the body associated with dream mentation during REM sleep that usually disturbs sleep continuity. During the nocturnal spells, patients behave as if they were acting out their dream, in the absence of muscle atonia [139]. This disease may be idiopathic (up to 20 %) but mostly associated with neurodegenerative disorders. A sizeable proportion of patients with RBD will develop extrapyramidal disorders [335–337], Lewy body dementia (LBD) [338], and multiple system atrophy (MSA) [339, 340]. More recently, a strong association between RBD and α-synucleinopathies has been observed, with the parasomnia often preceding the clinical onset of the neurodegenerative disease [338]. It is notable that, an early experimental model of RBD in the cat has shown that lesions in the mesopontine tegmentum can lead to the disappearance of muscle atonia during REM sleep together with dream-enactment behavior [341].

Functional Neuroimaging Studies of RBD

Changes in perfusion to various brain regions have been shown in a number of studies (Fig. 21.2e). A SPECT study in 8 RBD patients during waking rest showed decreased activity in the frontal and temporoparietal cortices but found increased activity in the pons, putamen, and right hippocampus [342]. These results have been verified in later studies with larger sample sizes [343, 344]. In another SPECT study, 24 idiopathic RBD patients showed decreased rCBF in cerebellar, parietal, occipital, and limbic regions [345].

A recent longitudinal study followed 20 idiopathic RBD patients over an average period of 3 years. At the study's outset, patients were scanned during wakefulness with ^{99m}Tc-ECD SPECT. After the three-year period, 10 of the patients had developed PD or LBD. Regression analysis revealed that hyperperfusion in the hippocampus predicted

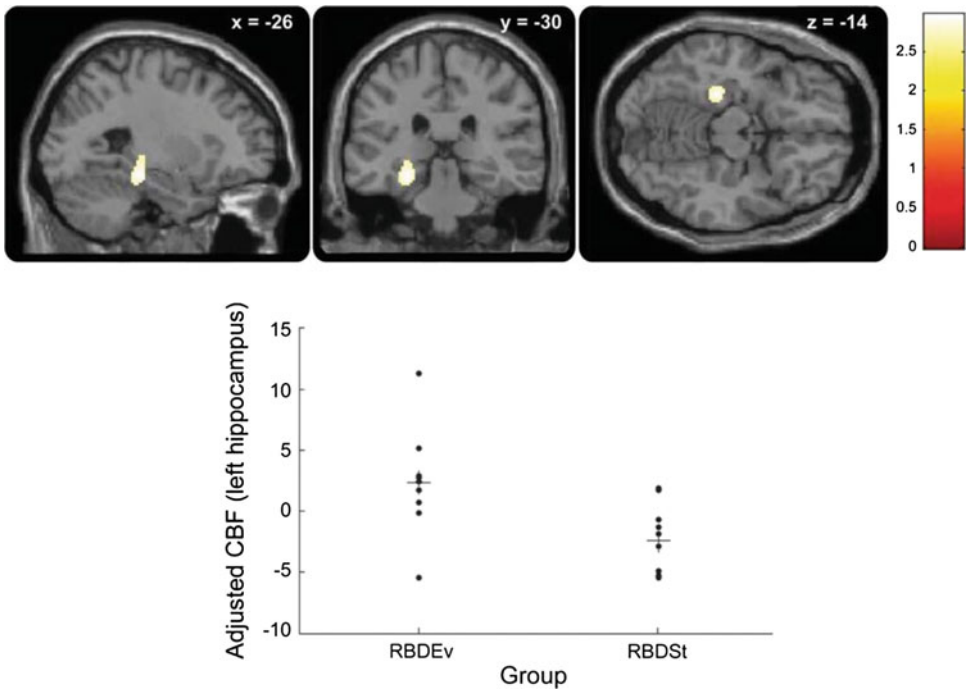

Fig. 21.7 Hippocampal hyperperfusion in REM sleep behavior disorder patients who did (RBDEv) and did not (RBDSt) develop synucleinopathy. Peak hypoperfusion of the left hippocampus at study outset is shown in sagittal, coronal, and transverse sections ($p< 0.05$ corrected). The range of t values for this contrast is shown in the *color scale* on the *right*. The coordinates are given at the *top right* corner of each panel. *Below*, the plot displays the adjusted regional cerebral blood flow in the left hippocampus, showing distinct distributions for RBDEv and RBDSt groups. Each subject is represented by a *black dot*. *Horizontal bars* represent group means (Reproduced with permission from Dang-Vu et al. [344]. Copyright 2012, American Academy of Neurology)

the subsequent development of LBD or PD in RBD patients (Fig. 21.7) [344]. Hippocampal perfusion across RBD patients was also correlated with motor and color vision scores, which are markers of neurodegeneration. This demonstrates the involvement of hippocampal perfusion as a consistent biomarker of the neurodegenerative evolution in RBD. Studies of brain perfusion with SPECT thus provide useful prognostic tools predicting the onset of neurodegenerative diseases in RBD patients.

One ^{99m}Tc-ECD SPECT study was able to capture an episode of RBD in an MSA patient [346]. Notably, perfusion to the supplementary motor area increased compared to wakefulness, while no such pattern was found during REM sleep in two healthy controls. However, REM sleep outside the episode was not imaged in the MSA patient, thus limiting conclusions about the specificity of supplementary motor area activation to dream enactment in RBD. Replication in larger samples, along with baseline REM sleep assessment, may determine whether this area plays a role in RBD pathophysiology.

Neurotransmission in RBD

Findings of RBD comorbidity with dopaminergic disorders, such as PD and LBD [344], have driven forward research into the nigrostriatal dopaminergic system in RBD patients. Presynaptic DAT densities have been probed in two SPECT studies with the DAT ligand ^{123}IPT [109, 347]. Together, they trace a spectrum of decreasing striatal DAT density from healthy subjects, to subclinical RBD patients showing muscle atonia with no dream enactment, to full-blown RBD patients, and finally to PD patients, who showed the lowest presynaptic DAT density. A similar spectrum was described by a third SPECT study using another presynaptic DAT ligand, ^{123}I-2β carbomethoxy-3 (4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (^{123}I-FP-CIT) [348]. In contrast, four more studies using this ligand reported striatal DAT decreases in only a minority of RBD patients (2 out of 11 [349], 2 out of 5 [350] and 3 out of 14 [348]). PET studies have also found striatal DAT decreases in RBD, using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), an in vivo marker for dopaminergic nerve terminals. Significant reductions in striatal ^{11}C-DTBZ binding characterized 6 elderly subjects with chronic idiopathic RBD, as compared to 19 age-matched controls, particularly in the posterior putamen [351].

Two longitudinal ^{123}I-FP-CIT SPECT studies, from the same research group, examined the relationship between striatal DAT and incident neurodegenerative disease over the course of several years [352, 353]. The first study followed 43 idiopathic RBD patients and 18 controls [352]. At the outset, 40 % of RBD patients showed reduced striatal DAT. Patients were followed up 2.5 years later and 8 of them had developed a neurodegenerative disorder (PD, LBD, or MSA). Six of these eight patients had shown reduced striatal DAT at the outset of the study. This measure may then provide a useful tool early on for identifying RBD patients at high risk for developing neurodegenerative disease. The second longitudinal study followed 44 idiopathic RBD patients over the course of 7 years [353]. At follow-up, 82 % of patients had developed a neurodegenerative disease. The 4 patients showing no sign of disease had reduced striatal DAT at follow-up, placing them at high risk of developing a neurodegenerative disease later on. Both studies buttressed the association between RBD and reduced presynaptic DAT in the SN, and provided additional evidence that idiopathic RBD presents an early stage of neurodegeneration. The deterioration of presynaptic dopamine dysfunction was monitored in a longitudinal case report of a 73-year-old male suffering from RBD over 3.5 years. ^{11}C-CFT with PET was used to show a significant decrease (about 4–6 % per year) in dopamine binding in the striatum, similar to decreases observed in PD [354]. It remains to be shown whether these dopaminergic alterations play a causal role in the pathophysiology of RBD or reflect functional consequences and adaptations to the pathologic conditions.

Lastly, postsynaptic D_2 receptor density was also assessed in RBD in two previously cited ^{123}I-IBZM SPECT studies from the same group [109, 347]. There were no significant differences detected between RBD, PD, and healthy control groups, indicating that postsynaptic dopaminergic function is unaltered in RBD.

Anatomic Neuroimaging Studies of RBD

Neuroanatomical abnormalities in RBD have been revealed by structural neuroimaging (Fig. 21.2e). One study, employing MRI and VBM, demonstrated decreased bilateral putamen volumes in RBD patients compared to healthy controls, as well as in comparison with patients with early PD [355]. A later study conducted through DTI whole-brain scans showed white matter microstructural changes in 12 patients with idiopathic RBD compared with age-matched healthy controls [356]. These significant changes occurred in multiple brain regions known to be involved in REM sleep regulation. Notably, changes were found in the pons. A combined DTI-VBM study [357] found white matter decreases in the pontine region, as well as significant bilateral gray matter increase in the hippocampus of RBD patients. Structural alterations in the pons and hippocampus are in accord with findings from functional studies described above [342, 344, 358, 359].

In addition, an increased Cho/Cr ratio in the brain stem suggesting local neural abnormalities was revealed by ^{1}H-MRS in a 69-year-old man with idiopathic RBD as compared with healthy adults [360]. In contrast, one ^{1}H-MRS study, conducted in 15 patients with idiopathic RBD and 15 matched control subjects, failed to reveal any difference in metabolic peaks of NAA/Cr, Cho/Cr, and myoinositol/creatine ratios in the pontine tegmentum and the midbrain [361]. Similarly, a ^{1}H-MRS study examining pontine metabolic ratios in 15 PD patients with RBD and 15 PD patients without RBD detected no group difference [362]. Whether

idiopathic RBD involves mesopontine neuronal loss or ^{1}H-MRS–detectable metabolic disturbances therefore remains unsettled.

Transcranial ultrasound has been employed to measure SN iron levels in RBD based on midbrain echogenicity. Since increased nigral iron concentrations are a reliable biomarker of PD, as evidenced by ultrasound hyperechogenicity, Iranzo et al. hypothesized that transcranial ultrasound measures of nigral iron in RBD may predict the later onset of PD and other synucleinopathies. In their aforementioned longitudinal study [352], they measured nigral iron levels in 39 idiopathic RBD patients and 149 controls, and found hyperechogenicity in 36 % of RBD patients and 11 % of controls. Two and a half years later, 8 of 43 RBD patients had developed synucleinopathies, 5 of which had shown hyperechogenicity at the study's outset. In combination with DAT concentration measures from ^{123}I-FP-CIT SPECT, this study was able to use transcranial ultrasound to predict the conversion from idiopathic RBD to synucleinopathy with 100 % sensitivity and 55 % specificity. Similar to the decreasing DAT spectrum described earlier, this study provides evidence for a spectrum of increasing iron concentrations in the SN, from normal levels, to RBD, and ending in synucleinopathy.

Summary

Structural and functional neuroimaging studies in RBD agree with involvement of the pons in the pathophysiology of RBD. In addition, presynaptic dopamine dysfunction in nigrostriatal pathways seems related to the progression of RBD severity, with subclinical RBD showing the least reduction in DAT density, followed by a greater reduction in manifest RBD, and the greatest reduction in neurodegenerative disease, particularly in synucleinopathies (PD, LBD, and MSA). Whether dopaminergic dysfunction is a cause or consequence of RBD remains unclear. Similar to the spectrum of decreasing striatal DAT density, transcranial ultrasound data suggest a spectrum of increasing iron concentrations in the SN from normal levels, to RBD, and ending in synucleinopathy. Early biomarkers seem available to identify RBD patients at high risk of developing a synucleinopathy, using transcranial ultrasound of the SN combined with SPECT assessing presynaptic striatal DAT density or hippocampal hyperperfusion. Future studies would do well to investigate hippocampal involvement in RBD, as well as provide additional functional data during sleep, particularly during RBD dream-enactment episodes.

Conclusions

The relatively new field of neuroimaging has already yielded valuable insights into disorders of sleep. Functional anomalies in brain activation in insomnia patients support hyperarousal theory, whereas structural alterations in the hippocampus, rACC and prefrontal cortex may underlie cognitive and emotional deficits in insomnia. Hypothalamic abnormalities in narcolepsy, both functional and structural, are consistent with a dysfunction of the hypocretinergic system. Altered response of the limbic system and anatomic alterations of the hippocampus and cortical areas may relate to emotional dysregulation in narcolepsy. Thalamic hypoperfusion pervades the few recurrent hypersomnia studies. A dysregulation of autonomic control seems to underlie OSAS, and cognitive deficits may be reflected in structural alterations of the prefrontal cortex, parietal cortex, hippocampus, and white matter tracts. Functional alterations also occur in OSAS, notably in the reduced connectivity of the default-mode network. While functional and structural changes seem partially reversible by CPAP, some cognitive deficits may be more permanent. Turning to movement disorders, RLS may be due to an imbalance in the sensorimotor control of pain, which itself may be due to dopaminergic dysfunction and iron depletion in the SN. The single case report of a sleepwalking episode showed prefrontal hypoperfusion and posterior cingulate hyperperfusion. Lastly, RBD seems to be related to pontine abnormalities, as evidenced by structural and functional studies. Presynaptic dopamine dysfunction in the striatum is also a reliable feature of RBD, correlating with the degradation from subclinical RBD, through full-blown RBD, and eventually to synucleinopathy. Neuroimaging may provide a valuable tool in identifying RBD patients at greatest risk of neurodegenerative disease, by relying on biomarkers such as DAT density, nigral hyperechogenicity, and hippocampal hyperperfusion.

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

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References

1. Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK (2005) Functional imaging of working memory in obstructive sleep-disordered breathing. J Appl Physiol 98(6):2226–2234 PubMed PMID: 15677733

2. Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R et al (2000) Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res 9(4):335–352 PubMed PMID: 11123521
3. Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R et al (2003) Neural basis of alertness and cognitive performance impairments during sleepiness. II. Effects of 48 and 72 h of sleep deprivation on waking human regional brain activity. Thalamus Relat Syst 2003 (2):199–229
4. Drummond SP, Brown GG, Stricker JL, Buxton RB, Wong EC, Gillin JC (1999) Sleep deprivation-induced reduction in cortical functional response to serial subtraction. NEUROREPORT 10 (18):3745–3748 PubMed PMID: 10716202
5. Desseilles M, Dang-Vu T, Schabus M, Sterpenich V, Maquet P, Schwartz S (2008) Neuroimaging insights into the pathophysiology of sleep disorders. Sleep 31(6):777–794 PubMed PMID: 18548822
6. Kryger MH, Roth T, Dement WC (2000) Principles and practice of sleep medicine, third edn. W.B. Saunders Company, Philadelphia, 1336 p
7. Steriade M, Amzica F (1998) Coalescence of sleep rhythms and their chronology in corticothalamic networks. Sleep Res Online 1 (1):1–10 PubMed PMID: 11382851
8. Maquet P (2000) Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 9(3):207–231 PubMed PMID: 11012860
9. Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R et al (1992) Cerebral glucose utilization during stage 2 sleep in man. Brain Res 571(1):149–153 PubMed PMID: 1611488
10. Madsen PL, Schmidt JF, Holm S, Vorstrup S, Lassen NA, Wildschiodtz G (1991) Cerebral oxygen metabolism and cerebral blood flow in man during light sleep (stage 2). Brain Res 557(1–2):217–220 PubMed PMID: 1747754
11. Kjaer TW, Law I, Wiltschiotz G, Paulson OB, Madsen PL (2002) Regional cerebral blood flow during light sleep–a H(2)(15) O-PET study. J Sleep Res 11(3):201–207 PubMed PMID: 12220315
12. Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R et al (1990) Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F] 2-fluoro-2-deoxy-D-glucose method. Brain Res 513(1):136–143 PubMed PMID: 2350676
13. Madsen PL, Schmidt JF, Wildschiodtz G, Friberg L, Holm S, Vorstrup S et al (1991) Cerebral O2 metabolism and cerebral blood flow in humans during deep and rapid-eye-movement sleep. J Appl Physiol 70(6):2597–2601 PubMed PMID: 1885454
14. Kajimura N, Uchiyama M, Takayama Y, Uchida S, Uema T, Kato M et al (1999) Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. J Neurosci 19(22):10065–10073 PubMed PMID: 10559414
15. Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P et al (1997) Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain J Neurol 120(Pt 7):1173–1197 PubMed PMID: 9236630
16. Maquet P, Degueldre C, Delfiore G, Aerts J, Peters JM, Luxen A et al (1997) Functional neuroanatomy of human slow wave sleep. J Neurosci 17(8):2807–2812 PubMed PMID: 9092602
17. Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, Price JC, Sembrat RC et al (2002) Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain J Neurol 125(Pt 5):1105–1115 PubMed PMID: 11960899
18. Hofle N, Paus T, Reutens D, Fiset P, Gotman J, Evans AC et al (1997) Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. J Neurosci 17(12):4800–4808 PubMed PMID: 9169538
19. Dang-Vu TT, Desseilles M, Laureys S, Degueldre C, Perrin F, Phillips C et al (2005) Cerebral correlates of delta waves during non-REM sleep revisited. Neuroimage 28(1):14–21 PubMed PMID: 15979343
20. Steriade M, Nunez A, Amzica F (1993) Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci 13 (8):3266–3283 PubMed PMID: 8340807
21. Finelli LA, Borbely AA, Achermann P (2001) Functional topography of the human nonREM sleep electroencephalogram. Eur J Neurosci 13(12):2282–2290 PubMed PMID: 11454032
22. Andersson JL, Onoe H, Hetta J, Lidstrom K, Valind S, Lilja A et al (1998) Brain networks affected by synchronized sleep visualized by positron emission tomography. J Cereb Blood Flow Metab 18(7):701–715 PubMed PMID: 9663500
23. Borbely AA (2001) From slow waves to sleep homeostasis: new perspectives. Arch Ital Biol 139(1–2):53–61 PubMed PMID: 11256187
24. Harrison Y, Horne JA (1999) One night of sleep loss impairs innovative thinking and flexible decision making. Organ Behav Hum Decis Process 78(2):128–145 PubMed PMID: 10329298
25. Schabus M, Dang-Vu TT, Albouy G, Balteau E, Boly M, Carrier J et al (2007) Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A 104(32):13164–13169 PubMed PMID: 17670944. Pubmed Central PMCID: 1941810. Epub 2007/08/03. eng
26. Dang-Vu TT, Schabus M, Desseilles M, Albouy G, Boly M, Darsaud A et al (2008) Spontaneous neural activity during human slow wave sleep. Proc Natl Acad Sci U S A 105(39):15160–15165 PubMed PMID: 18815373. Pubmed Central PMCID: 2567508. Epub 2008/09/26. eng
27. Eschenko O, Magri C, Panzeri S, Sara SJ (2012) Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. Cerebral Cortex 22(2):426–435 PubMed PMID: 21670101. Epub 2011/06/15. eng
28. Steriade M, McCarley RW (1990) Brainstem control of wakefulness and sleep. Plenum Press, New York
29. Jones BE (1991) Paradoxical sleep and its chemical/structural substrates in the brain. Neuroscience 40(3):637–656 PubMed PMID: 2062436
30. Lenzi P, Zoccoli G, Walker AM, Franzini C (1999) Cerebral blood flow regulation in REM sleep: a model for flow-metabolism coupling. Arch Ital Biol 137(2–3):165–179 PubMed PMID: 10349495
31. Maquet P, Peters J, Aerts J, Delfiore G, Degueldre C, Luxen A et al (1996) Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383(6596):163–166 PubMed PMID: 8774879
32. Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, Moore RY (1997) Forebrain activation in REM sleep: an FDG PET study. Brain Res 770(1–2):192–201 PubMed PMID: 9372219
33. Braun AR, Balkin TJ, Wesensten NJ, Gwadry F, Carson RE, Varga M et al (1998) Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 279(5347):91–95 PubMed PMID: 9417032
34. Maquet P, Phillips C (1998) Functional brain imaging of human sleep. J Sleep Res 7(Suppl 1):42–47 PubMed PMID: 9682193
35. Chow HM, Horovitz SG, Carr WS, Picchioni D, Coddington N, Fukunaga M et al (2013) Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of

consciousness. Proc Natl Acad Sci U S A 110(25):10300–10305 PubMed PMID: 23733938. Pubmed Central PMCID: 3690889
36. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98(2):676–682 PubMed PMID: 11209064
37. Datta S, Siwek DF, Patterson EH, Cipolloni PB (1998) Localization of pontine PGO wave generation sites and their anatomical projections in the rat. Synapse 30(4):409–423 PubMed PMID: 9826233
38. Jouvet M (1967) Neurophysiology of the states of sleep. Physiol Rev 47(2):117–177 PubMed PMID: 5342870
39. Mikiten T, Niebyl P, Hendley C (1961) EEG desynchronization during behavioural sleep associated with spike discharges from the thalamus of the cat. Fed Proc 20:327
40. Mouret J, Jeannerod M, Jouvet M (1963) Electrical activity of the visual system during the paradoxical phase of sleep in the cat. J Physiol (Paris) 55:305–306 PubMed PMID: 13936360
41. Hobson JA (1964) The phasic electrical activity of the cortex and thalamus during desynchronized sleep in cats. C R Seances Soc Biol Fil1 58:2131–2135 PubMed PMID: 14282131. L'activit'e 'electrique phasique du cortex et du thalamus au cours du sommeil d'esynchronis'e chez le chat
42. Salzarulo P, Lairy GC, Bancaud J, Munari C, Barros0Ferreira MD (1975) Direct depth recording of the striate cortex during REM sleep in man: are there PGO potentials? Electroencephalogr Clin Neurophysiol 38(2):199–202 PubMed PMID: 45953
43. McCarley RW, Winkelman JW, Duffy FH (1983) Human cerebral potentials associated with REM sleep rapid eye movements: links to PGO waves and waking potentials. Brain Res 274 (2):359–364 PubMed PMID: 6626965
44. Ioannides AA, Corsi-Cabrera M, Fenwick PB, del Rio Portilla Y, Laskaris NA, Khurshudyan A et al (2004) MEG tomography of human cortex and brainstem activity in waking and REM sleep saccades. Cereb Cortex 14(1):56–72 PubMed PMID: 14654457
45. Inoue S, Saha U, Musha T (1999) Spatio-temporal distribution of neuronal activities and REM sleep. In: Mallick B, Inoue S (eds) Rapid eye movement sleep. Narosa Publishing House, New Dehli, pp 214–230
46. Peigneux P, Laureys S, Fuchs S, Delbeuck X, Degueldre C, Aerts J et al (2001) Generation of rapid eye movements during paradoxical sleep in humans. Neuroimage 14(3):701–708
47. Miyauchi S, Misaki M, Kan S, Fukunaga T, Koike T (2009) Human brain activity time-locked to rapid eye movements during REM sleep. Exp Brain Res 192(4):657–667 PubMed PMID: 18830586. Epub 2008/10/03. eng
48. Wehrle R, Czisch M, Kaufmann C, Wetter TC, Holsboer F, Auer DP et al (2005) Rapid eye movement-related brain activation in human sleep: a functional magnetic resonance imaging study. Neuroreport 16(8):853–857 PubMed PMID: 15891584
49. Dang-Vu TT, Schabus M, Cologan V, Maquet P (2009) Sleep: implications for theories of dreaming and consciousness. In: Banks WP (ed) Encyclopedia of consciousness, vol 2. Elsevier, Oxford, p 357–373
50. Schwartz S, Maquet P (2002) Sleep imaging and the neuro-psychological assessment of dreams. Trends Cogn Sci. 6 (1):23–30 PubMed PMID: 11849612
51. Dresler M, Wehrle R, Spoormaker VI, Koch SP, Holsboer F, Steiger A et al (2012) Neural correlates of dream lucidity obtained from contrasting lucid versus non-lucid REM sleep: a combined EEG/fMRI case study. Sleep 35(7):1017–1020 PubMed PMID: 22754049. Pubmed Central PMCID: 3369221
52. Dresler M, Koch SP, Wehrle R, Spoormaker VI, Holsboer F, Steiger A et al (2011) Dreamed movement elicits activation in the sensorimotor cortex. Curr Biol 21(21):1833–1837 PubMed PMID: 22036177
53. Perrin F, Garcia-Larrea L, Mauguiere F, Bastuji H (1999) A differential brain response to the subject's own name persists during sleep. Clin Neurophysiol 110(12):2153–2164 PubMed PMID: 10616121
54. Bonnet M (1982) Performance during sleep. In: Webb WB (ed) Biological rhythms, sleep and performance. Wiley, Chichester, pp 205–237
55. Portas CM, Krakow K, Allen P, Josephs O, Armony JL, Frith CD (2000) Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. Neuron 28 (3):991–999 PubMed PMID: 11163282
56. Czisch M, Wehrle R, Stiegler A, Peters H, Andrade K, Holsboer F et al (2009) Acoustic oddball during NREM sleep: a combined EEG/fMRI study. PLoS ONE 4(8):e6749 PubMed PMID: 19707599. Pubmed Central PMCID: 2727699. Epub 2009/08/27. eng
57. Czisch M, Wetter TC, Kaufmann C, Pollmacher T, Holsboer F, Auer DP (2002) Altered processing of acoustic stimuli during sleep: reduced auditory activation and visual deactivation detected by a combined fMRI/EEG study. Neuroimage 16 (1):251–258 PubMed PMID: 11969332
58. Born AP, Law I, Lund TE, Rostrup E, Hanson LG, Wildschiodtz G et al (2002) Cortical deactivation induced by visual stimulation in human slow-wave sleep. NeuroImage 17(3):1325–1335 PubMed PMID: 12414272
59. Czisch M, Wehrle R, Kaufmann C, Wetter TC, Holsboer F, Pollmacher T et al (2004) Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. Eur J Neurosci 20(2):566–574 PubMed PMID: 15233766
60. Wehrle R, Kaufmann C, Wetter TC, Holsboer F, Auer DP, Pollmacher T et al (2007) Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. Eur J Neurosci 25 (3):863–871 PubMed PMID: 17328781. eng
61. Dang-Vu TT, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M et al (2011) Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A 108(37):15438–15443 PubMed PMID: 21896732. Epub 2011/09/08. eng
62. Dang-Vu TT, McKinney SM, Buxton OM, Solet JM, Ellenbogen JM (2010) Spontaneous brain rhythms predict sleep stability in the face of noise. Curr Biol 20(15):R626–R627 PubMed PMID: 20692606. Epub 2010/08/10. eng
63. Andrade KC, Spoormaker VI, Dresler M, Wehrle R, Holsboer F, Samann PG et al (2011) Sleep spindles and hippocampal functional connectivity in human NREM sleep. J Neurosci 31(28):10331–10339 PubMed PMID: 21753010. Epub 2011/07/15. eng
64. Schabus M, Dang-Vu TT, Heib DP, Boly M, Desseilles M, Vandewalle G et al (2012) The Fate of Incoming Stimuli during NREM Sleep is determined by spindles and the phase of the slow oscillation. Front Neurol 3:40 PubMed PMID: 22493589. Pubmed Central PMCID: 3319907. Epub 2012/04/12. eng
65. Maquet P, Smith C, Stickgold R (2003) Sleep and brain plasticity. Oxford University Press, Oxford
66. Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C et al (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3(8):831–836 PubMed PMID: 10903578
67. Peigneux P, Laureys S, Fuchs S, Destrebecqz A, Collette F, Delbeuck X et al (2003) Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. Neuroimage 20(1):125–134 PubMed PMID: 14527575

68. Laureys S, Peigneux P, Phillips C, Fuchs S, Degueldre C, Aerts J et al (2001) Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep. Neuroscience 105(3):521–525
69. Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J et al (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44(3):535–545 PubMed PMID: 15504332
70. Plihal W, Born J (1999) Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 36(5):571–582 PubMed PMID: 10442025
71. Smith C (1995) Sleep states and memory processes. Behav Brain Res 69(1–2):137–145 PubMed PMID: 7546305
72. Maquet P, Schwartz S, Passingham R, Frith C (2003) Sleep-related consolidation of a visuomotor skill: brain mechanisms as assessed by functional magnetic resonance imaging. J Neurosci 23(4):1432–1440 PubMed PMID: 12598632
73. Krauzlis RJ, Stone LS (1999) Tracking with the mind's eye. Trends Neurosci 22(12):544–550 PubMed PMID: 10542434
74. Orban P, Rauchs G, Balteau E, Degueldre C, Luxen A, Maquet P et al (2006) Sleep after spatial learning promotes covert reorganization of brain activity. Proc Natl Acad Sci U S A 103 (18):7124–7129 PubMed PMID: 16636288
75. Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M et al (2007) Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci U S A 104(47):18778–10783 PubMed PMID: 18000060. Pubmed Central PMCID: 2141853. Epub 2007/11/15. eng
76. Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A, Balteau E et al (2007) Sleep-related hippocampo-cortical interplay during emotional memory recollection. PLoS Biol 5(11): e282 PubMed PMID: 17958471
77. Takashima A, Nieuwenhuis ILC, Jensen O, Talamini LM, Rijpkema M, Fernandez G (2009) Shift from hippocampal to neocortical centered retrieval network with consolidation. J Neurosci 29(32):10087–10093 PubMed PMID: 1155
78. Rasch B, Buchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315(5817):1426–1429 PubMed PMID: 17347444
79. van Dongen EV, Takashima A, Barth M, Zapp J, Schad LR, Paller KA et al (2012) Memory stabilization with targeted reactivation during human slow-wave sleep. Proc Natl Acad Sci U S A 109(26):10575–10580 PubMed PMID: 22691500. Pubmed Central PMCID: 3387124
80. Gais S, Molle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22(15):6830–6834 PubMed PMID: 12151563
81. Smith C, MacNeill C (1994) Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. J Sleep Res 3(4):206–213 PubMed PMID: 10607127
82. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35(1):205–211 PubMed PMID: 12123620
83. Schabus M, Gruber G, Parapatics S, Sauter C, Klosch G, Anderer P et al (2004) Sleep spindles and their significance for declarative memory consolidation. Sleep 27(8):1479–1485 PubMed PMID: 15683137
84. Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430(6995):78–81 PubMed PMID: 15184907
85. Smith CT, Nixon MR, Nader RS (2004) Posttraining increases in REM sleep intensity implicate REM sleep in memory processing and provide a biological marker of learning potential. Learn Mem 11(6):714–719 PubMed PMID: 15576889
86. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613 PubMed PMID: 17086200
87. Bergmann TO, Molle M, Diedrichs J, Born J, Siebner HR (2011) Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. NeuroImage 59 (3):2733–2742 PubMed PMID: 22037418. Epub 2011/11/01. eng
88. Horne JA, Reyner LA (1995) Sleep related vehicle accidents. BMJ 310(6979):565–567 PubMed PMID: 7888930
89. Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Hazlett E, Sicotte N et al (1991) The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. Sleep 14(2):155–162 PubMed PMID: 1866529
90. Thomas ML, SIng HC, Belenky G, Holcomb HH, Mayberg HS, Dannals RF et al (2003) Neural basis of alertness and cognitive performance impairments during sleepiness. II. Effects of 48 and 72 hours of sleep deprivation on waking human regional brain activity. Thalamus Relat Syst 2:199–229
91. Horne JA (1993) Human sleep, sleep loss and behaviour. Implications for the prefrontal cortex and psychiatric disorder. Br J Psychiatry 162:413–419 PubMed PMID: 8453439
92. Mu Q, Nahas Z, Johnson KA, Yamanaka K, Mishory A, Koola J et al (2005) Decreased cortical response to verbal working memory following sleep deprivation. Sleep 28(1):55–67 PubMed PMID: 15700721
93. Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB (2000) Altered brain response to verbal learning following sleep deprivation. Nature 403(6770):655–657 PubMed PMID: 10688201
94. Chee MW, Choo WC (2004) Functional imaging of working memory after 24 hr of total sleep deprivation. J Neurosci 24 (19):4560–4567 PubMed PMID: 15140927
95. Choo WC, Lee WW, Venkatraman V, Sheu FS, Chee MW (2005) Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. Neuroimage 25(2):579–587 PubMed PMID: 15784437. Epub 2005/03/24. eng
96. Drummond SP, Brown GG, Salamat JS, Gillin JC (2004) Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. Sleep 27(3):445–451 PubMed PMID: 15164897
97. Tomasi D, Wang RL, Telang F, Boronikolas V, Jayne MC, Wang GJ et al (2009) Impairment of attentional networks after 1 night of sleep deprivation. Cereb Cortex 19(1):233–240 PubMed PMID: 18483003. Pubmed Central PMCID: 2638746
98. Muto V, Shaffii-le Bourdiec A, Matarazzo L, Foret A, Mascetti L, Jaspar M et al (2012) Influence of acute sleep loss on the neural correlates of alerting, orientating and executive attention components. J Sleep Res 21(6):648–658 PubMed PMID: 22594455
99. Drummond SP, Meloy MJ, Yanagi MA, Orff HJ, Brown GG (2005) Compensatory recruitment after sleep deprivation and the relationship with performance. Psychiatry Res 140(3):211–223 PubMed PMID: 16263248
100. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ (2009) Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 33 (3):279–296 PubMed PMID: 18824195
101. Gujar N, Yoo SS, Hu P, Walker MP (2010) The unrested resting brain: sleep deprivation alters activity within the default-mode network. J Cogn Neurosci 22(8):1637–1648 PubMed PMID: 19702469. Pubmed Central PMCID: 2883887
102. De Havas JA, Parimal S, Soon CS, Chee MW (2012) Sleep deprivation reduces default mode network connectivity and

anti-correlation during rest and task performance. Neuroimage 59 (2):1745–1751 PubMed PMID: 21872664
103. Samann PG, Tully C, Spoormaker VI, Wetter TC, Holsboer F, Wehrle R et al (2010) Increased sleep pressure reduces resting state functional connectivity. Magma. 23(5–6):375–389 PubMed PMID: 20473549
104. Venkatraman V, Chuah YM, Huettel SA, Chee MW (2007) Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. Sleep 30(5):603–609 PubMed PMID: 17552375
105. Venkatraman V, Huettel SA, Chuah LY, Payne JW, Chee MW (2011) Sleep deprivation biases the neural mechanisms underlying economic preferences. J Neurosci 31(10):3712–3718 PubMed PMID: 21389226
106. Rosales-Lagarde A, Armony JL, Del Rio-Portilla Y, Trejo-Martinez D, Conde R, Corsi-Cabrera M (2012) Enhanced emotional reactivity after selective REM sleep deprivation in humans: an fMRI study. Front Behav Neurosci 6:25 PubMed PMID: 22719723. Epub 2012/06/22. eng
107. Killgore WD, McBride SA (2006) Odor identification accuracy declines following 24 h of sleep deprivation. J Sleep Res 15 (2):111–116 PubMed PMID: 16704564
108. Benedict C, Brooks SJ, O'Daly OG, Almen MS, Morell A, Aberg K et al (2012) Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. J Clin Endocrinol Metab 97(3):E443–E447 PubMed PMID: 22259064
109. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K (2000) Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. Brain J Neurol 123 (Pt 6):1155–1160 PubMed PMID: 10825354
110. Happe S, Tings T, Koch W, Welsch J, Helmschmied K, Baier PC et al (2007) Growth hormone response in low-dose apomorphine test correlates with nigrostriatal dopamine transporter binding in patients with Parkinson's disease. J Neural Transm 114(5):589–594 PubMed PMID: 17187291
111. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C et al (2008) Sleep deprivation decreases binding of [^{11}C] raclopride to dopamine D2/D3 receptors in the human brain. J Neurosci 28(34):8454–8461 PubMed PMID: 18716203. Pubmed Central PMCID: 2710773
112. Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Wang RL et al (2009) Hyperstimulation of striatal D2 receptors with sleep deprivation: Implications for cognitive impairment. Neuroimage 45(4):1232–1240 PubMed PMID: 19349237. Pubmed Central PMCID: 2714585
113. Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Logan J et al (2012) Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. J Neurosci 32(19):6711–6717 PubMed PMID: 22573693. Pubmed Central PMCID: 3433285
114. Martins RC, Andersen ML, Garbuio SA, Bittencourt LR, Guindalini C, Shih MC et al (2010) Dopamine transporter regulation during four nights of REM sleep deprivation followed by recovery–an in vivo molecular imaging study in humans. Sleep 33(2):243–251 PubMed PMID: 20175408. Pubmed Central PMCID: 2817911
115. Mu Q, Mishory A, Johnson KA, Nahas Z, Kozel FA, Yamanaka K et al (2005) Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. Sleep 28(4):433–446 PubMed PMID: 16171288
116. Caldwell JA, Mu Q, Smith JK, Mishory A, Caldwell JL, Peters G et al (2005) Are individual differences in fatigue vulnerability related to baseline differences in cortical activation? Behav Neurosci 119(3):694–707 PubMed PMID: 15998190
117. Chee MW, Chuah LY, Venkatraman V, Chan WY, Philip P, Dinges DF (2006) Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. Neuroimage 31(1):419–428 PubMed PMID: 16427321. Epub 2006/01/24. eng
118. Chuah YM, Venkatraman V, Dinges DF, Chee MW (2006) The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. J Neurosci 26(27):7156–7162 PubMed PMID: 16822972
119. Rocklage M, Williams V, Pacheco J, Schnyer DM. White matter differences predict cognitive vulnerability to sleep deprivation. Sleep 32(8):1100–1103 PubMed PMID: 19725262. Pubmed Central PMCID: 2717201. Epub 2009/09/04. eng
120. Ziegler DA, Piguet O, Salat DH, Prince K, Connally E, Corkin S (2010) Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. Neurobiol Aging 31 (11):1912–1926 PubMed PMID: 19091444. Pubmed Central PMCID: 2996721
121. Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Johnson JC, Bunney WE Jr (1992) Effect of sleep deprivation on brain metabolism of depressed patients. Am J Psychiatry 149(4):538–543 PubMed PMID: 1554042
122. Wu JC, Gillin JC, Buchsbaum MS, Schachat C, Darnall LA, Keator DB et al (2008) Sleep deprivation PET correlations of Hamilton symptom improvement ratings with changes in relative glucose metabolism in patients with depression. J Affect Disord 107(1–3):181–186 PubMed PMID: 18031825
123. Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M et al (1999) Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry 156(8):1149–1158 PubMed PMID: 10450253
124. Ebert D, Feistel H, Barocka A (1991) Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tc-99 m-HMPAO SPECT. Psychiatry Res 40(4):247–251 PubMed PMID: 1811242
125. Ebert D, Feistel H, Barocka A, Kaschka W (1994) Increased limbic blood flow and total sleep deprivation in major depression with melancholia. Psychiatry Res 55(2):101–109 PubMed PMID: 10711798
126. Clark CP, Frank LR, Brown GG (2001) Sleep deprivation, EEG, and functional MRI in depression: preliminary results. Neuropsychopharmacology 25(5 Suppl):S79–S84 PubMed PMID: 11682279
127. Smith GS, Reynolds CF 3rd, Pollock B, Derbyshire S, Nofzinger E, Dew MA et al (1999) Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. Am J Psychiatry 156(5):683–689 PubMed PMID: 10327899
128. Smith GS, Reynolds CF, 3rd, Houck PR, Dew MA, Ginsberg J, Ma Y et al (2009) Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression: a randomized, placebo-controlled study. Psychiatry Res 171(1):1–9 PubMed PMID: 19087899. Pubmed Central PMCID: 2878400
129. Benedetti F, Calabrese G, Bernasconi A, Cadioli M, Colombo C, Dallaspezia S et al (2009) Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. Psychiatry Res 173(3):238–242 PubMed PMID: 19682864
130. Hefti K, Holst SC, Sovago J, Bachmann V, Buck A, Ametamey SM et al (2013) Increased metabotropic glutamate receptor subtype 5 availability in human brain after one night

without sleep. Biol Psychiatry 73(2):161–168 PubMed PMID: 22959709
131. Elmenhorst D, Kroll T, Matusch A, Bauer A (2012) Sleep deprivation increases cerebral serotonin 2A receptor binding in humans. Sleep 35(12):1615–23 PubMed PMID: 23204604. Pubmed Central PMCID: 3490354
132. Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A (1994) Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation—preliminary results. Biol Psychiatry 35 (11):880–885 PubMed PMID: 8054411
133. Gujar N, Yoo SS, Hu P, Walker MP (2011) Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. J Neurosci 31 (12):4466–4474 PubMed PMID: 21430147. Pubmed Central PMCID: 3086142
134. Dorsey CM, Lukas SE, Moore CM, Tartarini WL, Parow AM, Villafuerte RA et al (2003) Phosphorous31 magnetic resonance spectroscopy after total sleep deprivation in healthy adult men. Sleep 26(5):573–577 PubMed PMID: 12938810
135. Murashita J, Yamada N, Kato T, Tazaki M, Kato N (1999) Effects of sleep deprivation: the phosphorus metabolism in the human brain measured by 31P-magnetic resonance spectroscopy. Psychiatry Clin Neurosci 53(2):199–201 PubMed PMID: 10459688
136. Bernier D, Bartha R, Devarajan S, Macmaster FP, Schmidt MH, Rusak B (2009) Effects of overnight sleep restriction on brain chemistry and mood in women with unipolar depression and healthy controls. J Psychiatry Neurosci JPN 34(5):352–360 PubMed PMID: 19721845. Pubmed Central PMCID: 2732741
137. Luber B, Stanford AD, Bulow P, Nguyen T, Rakitin BC, Habeck C et al (2008) Remediation of sleep-deprivation-induced working memory impairment with fMRI-guided transcranial magnetic stimulation. Cereb Cortex 18(9):2077–2085 PubMed PMID: 18203694. Pubmed Central PMCID: 2981026. Epub 2008/01/22. eng
138. Luber B, Steffener J, Tucker A, Habeck C, Peterchev AV, Deng ZD et al (2013) Extended remediation of sleep deprived-induced working memory deficits using fMRI-guided transcranial magnetic stimulation. Sleep 36(6):857–871 PubMed PMID: 23729929. Pubmed Central PMCID: 3649828
139. AASM (2001) International classification of sleep disorders. Diagnostic and coding manual. American Academy of Sleep Medicine, Chicago, Illinois
140. Bonnet MH, Arand DL (1995) 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep 18(7):581–588 PubMed PMID: 8552929
141. Bonnet MH, Arand DL (1997) Hyperarousal and insomnia. Sleep Med Rev 1(2):97–108 PubMed PMID: 15310517
142. Stepanski E, Zorick F, Roehrs T, Young D, Roth T (1988) Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. Sleep 11(1):54–60 PubMed PMID: 3363270
143. Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE (2001) Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep 24(1):110–117 PubMed PMID: 11204046. Epub 2001/02/24. eng
144. Smith MT, Perlis ML, Chengazi VU, Pennington J, Soeffing J, Ryan JM et al (2002) Neuroimaging of NREM sleep in primary insomnia: a Tc-99-HMPAO single photon emission computed tomography study. Sleep 25(3):325–335 PubMed PMID: 12003163
145. Smith MT, Perlis ML, Chengazi VU, Soeffing J, McCann U (2005) NREM sleep cerebral blood flow before and after behavior therapy for chronic primary insomnia: preliminary single photon emission computed tomography (SPECT) data. Sleep Med 6(1):93–94 PubMed PMID: 15680307
146. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ (2004) Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 161(11):2126–2128 PubMed PMID: 15514418
147. Nofzinger EA, Nissen C, Germain A, Moul D, Hall M, Price JC et al (2006) Regional cerebral metabolic correlates of WASO during NREM sleep in insomnia. J Clin Sleep Med 2(3):316–322 PubMed PMID: 17561544. Epub 2007/06/15. eng
148. Altena E, Van Der Werf YD, Sanz-Arigita EJ, Voorn TA, Rombouts SA, Kuijer JP et al (2008) Prefrontal hypoactivation and recovery in insomnia. Sleep 31(9):1271–1276
149. Drummond SP, Walker M, Almklov E, Campos M, Anderson DE, Straus LD (2013) Neural correlates of working memory performance in primary insomnia. Sleep 36(9):1307–1316 PubMed PMID: 23997363. Pubmed Central PMCID: 3738039
150. Baglioni C, Spiegelhalder K, Lombardo C, Riemann D (2010) Sleep and emotions: a focus on insomnia. Sleep Med Rev 14 (4):227–238 PubMed PMID: 20137989
151. Huang Z, Liang P, Jia X, Zhan S, Li N, Ding Y et al (2012) Abnormal amygdala connectivity in patients with primary insomnia: evidence from resting state fMRI. Eur J Radiol 81 (6):1288–1295 PubMed PMID: 21458943
152. Riemann D, Voderholzer U, Spiegelhalder K, Hornyak M, Buysse DJ, Nissen C et al (2007) Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. Sleep 30 (8):955–958 PubMed PMID: 17702263
153. Winkelman JW, Benson KL, Buxton OM, Lyoo IK, Yoon S, O'Connor S et al (2010) Lack of hippocampal volume differences in primary insomnia and good sleeper controls: an MRI volumetric study at 3 Tesla. Sleep Med 11(6):576–582 PubMed PMID: 20466585
154. Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D et al (2012) The Relationship between hippocampal volume and cognition in patients with chronic primary insomnia. J Clin Neurol 8(2):130–138 PubMed PMID: 22787497. Pubmed Central PMCID: 3391618. Epub 2012/07/13. eng
155. Spiegelhalder K, Regen W, Baglioni C, Kloppel S, Abdulkadir A, Hennig J et al (2013) Insomnia does not appear to be associated with substantial structural brain changes. Sleep 36(5):731–737 PubMed PMID: 23633756. Pubmed Central PMCID: 3624828
156. Altena E, Vrenken H, Van Der Werf YD, van den Heuvel OA, Van Someren EJ (2010) Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. Biol Psychiatry 67(2):182–185 PubMed PMID: 19782344. Epub 2009/09/29. eng
157. Winkelman JW, Plante DT, Schoerning L, Benson K, Buxton OM, O'Connor SP et al (2013) Increased rostral anterior cingulate cortex volume in chronic primary insomnia. Sleep 36(7):991–998 PubMed PMID: 23814335. Pubmed Central PMCID: 3669070
158. Plante DT, Jensen JE, Schoerning L, Winkelman JW (2012) Reduced gamma-aminobutyric acid in occipital and anterior cingulate cortices in primary insomnia: a link to major depressive disorder? Neuropsychopharmacology 37(6):1548–1557 PubMed PMID: 22318195. Pubmed Central PMCID: 3327859
159. Joo EY, Noh HJ, Kim JS, Koo DL, Kim D, Hwang KJ et al (2013) Brain gray matter deficits in patients with chronic primary insomnia. Sleep 36(7):999–1007 PubMed PMID: 23814336. Pubmed Central PMCID: 3669067
160. Winkelman JW, Buxton OM, Jensen JE, Benson KL, O'Connor SP, Wang W et al (2008) Reduced brain GABA in primary insomnia: preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS). Sleep 31(11):1499–1506 PubMed PMID: 19014069. Pubmed Central PMCID: 2579978

161. Morgan PT, Pace-Schott EF, Mason GF, Forselius E, Fasula M, Valentine GW et al (2012) Cortical GABA levels in primary insomnia. Sleep 35(6):807–814 PubMed PMID: 22654200. Pubmed Central PMCID: 3353043
162. Harper DG, Plante DT, Jensen JE, Ravichandran C, Buxton OM, Benson KL et al (2013) Energetic and cell membrane metabolic products in patients with primary insomnia: a 31-phosphorus magnetic resonance spectroscopy study at 4 tesla. Sleep 36 (4):493–500 PubMed PMID: 23564996. Pubmed Central PMCID: 3612248
163. Baumann CR, Khatami R, Werth E, Bassetti CL. Hypocretin (orexin) deficiency predicts severe objective excessive daytime sleepiness in narcolepsy with cataplexy. J Neurol Neurosurg Psychiatry 77(3):402–404 PubMed PMID: 16484654. Pubmed Central PMCID: 2077721. Epub 2006/02/18. eng
164. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92(5):1 page following 696 PubMed PMID: 9527442
165. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y et al (2000) A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 6(9):991–997 PubMed PMID: 10973318
166. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M et al (2000) Reduced number of hypocretin neurons in human narcolepsy. Neuron 27(3):469–474 PubMed PMID: 11055430
167. Plazzi G, Montagna P, Provini F, Bizzi A, Cohen M, Lugaresi E (1996) Pontine lesions in idiopathic narcolepsy. Neurology 46 (5):1250–1254 PubMed PMID: 8628461
168. Bassetti C, Aldrich MS, Quint DJ (1997) MRI findings in narcolepsy. Sleep 20(8):630–631 PubMed PMID: 9351130
169. Frey JL, Heiserman JE (1997) Absence of pontine lesions in narcolepsy. Neurology 48(4):1097–1099 PubMed PMID: 9109908
170. Overeem S, Steens SC, Good CD, Ferrari MD, Mignot E, Frackowiak RS et al (2003) Voxel-based morphometry in hypocretin-deficient narcolepsy. Sleep 26(1):44–46 PubMed PMID: 12627731
171. Joo EY, Tae WS, Kim ST, Hong SB (2009) Gray matter concentration abnormality in brains of narcolepsy patients. Korean J Radiol 10(6):552–558 PubMed PMID: 19885310. Pubmed Central PMCID: 2770823. Epub 2009/11/04. eng
172. Kim SJ, Lyoo IK, Lee YS, Lee JY, Yoon SJ, Kim JE et al (2009) Gray matter deficits in young adults with narcolepsy. Acta Neurol Scand 119(1):61–67 PubMed PMID: 18624787. Epub 2008/07/16. eng
173. Scherfler C, Frauscher B, Schocke M, Nocker M, Gschliesser V, Ehrmann L et al (2012) White and gray matter abnormalities in narcolepsy with cataplexy. Sleep 35(3):345–351 PubMed PMID: 22379240. Epub 2012/03/02. eng
174. Brenneis C, Brandauer E, Frauscher B, Schocke M, Trieb T, Poewe W et al (2005) Voxel-based morphometry in narcolepsy. Sleep Med 6:531 PubMed PMID: 15994127
175. Kaufmann C, Schuld A, Pollmacher T, Auer DP (2002) Reduced cortical gray matter in narcolepsy: preliminary findings with voxel-based morphometry. Neurology 58(12):1852–1855 PubMed PMID: 12084891
176. Draganski B, Geisler P, Hajak G, Schuierer G, Bogdahn U, Winkler J et al (2002) Hypothalamic gray matter changes in narcoleptic patients. Nat Med 8(11):1186–1188 PubMed PMID: 12411926
177. Buskova J, Vaneckova M, Sonka K, Seidl Z, Nevsimalova S (2006) Reduced hypothalamic gray matter in narcolepsy with cataplexy. Neuro Endocrinol Lett 27(6):769–772 PubMed PMID: 17187022. eng
178. Joo EY, Kim SH, Kim ST, Hong SB (2012) Hippocampal volume and memory in narcoleptics with cataplexy. Sleep Med 13(4):396–401 PubMed PMID: 22361297. Epub 2012/03/01. eng
179. Brabec J, Rulseh A, Horinek D, Pala A, Guerreiro H, Buskova J et al (2011) Volume of the amygdala is reduced in patients with narcolepsy—a structural MRI study. Neuro Endocrinol Lett 32 (5):652–656 PubMed PMID: 22167152. Epub 2011/12/15. eng
180. Joo EY, Jeon S, Lee M, Kim ST, Yoon U, Koo DL et al (2011) Analysis of cortical thickness in narcolepsy patients with cataplexy. Sleep 34(10):1357–1364 PubMed PMID: 21966067. Pubmed Central PMCID: 3174837. Epub 2011/10/04. eng
181. Schaer M, Poryazova R, Schwartz S, Bassetti CL, Baumann CR (2012) Cortical morphometry in narcolepsy with cataplexy. J Sleep Res 21(5):487–494 PubMed PMID: 22309460. Epub 2012/02/09. eng
182. Menzler K, Belke M, Unger MM, Ohletz T, Keil B, Heverhagen JT et al (2012) DTI reveals hypothalamic and brainstem white matter lesions in patients with idiopathic narcolepsy. Sleep Med 13(6):736–742 PubMed PMID: 22541810. Epub 2012/05/01. eng
183. Lodi R, Tonon C, Vignatelli L, Iotti S, Montagna P, Barbiroli B et al (2004) In vivo evidence of neuronal loss in the hypothalamus of narcoleptic patients. Neurology 63(8):1513–1515 PubMed PMID: 15505179
184. Ellis CM, Simmons A, Lemmens G, Williams SC, Parkes JD (1998) Proton spectroscopy in the narcoleptic syndrome. Is there evidence of a brainstem lesion? Neurology 50(2 Suppl 1):S23–S26 PubMed PMID: 9484419. eng
185. Meyer JS, Sakai F, Karacan I, Derman S, Yamamoto M (1980) Sleep apnea, narcolepsy, and dreaming: regional cerebral hemodynamics. Ann Neurol 7(5):479–485 PubMed PMID: 7396426. eng
186. Meyer JS, Ishikawa Y, Hata T, Karacan I (1987) Cerebral blood flow in normal and abnormal sleep and dreaming. Brain Cogn 6 (3):266–294 PubMed PMID: 3606861
187. Asenbaum S, Zeithofer J, Saletu B, Frey R, Brucke T, Podreka I et al (1995) Technetium-99 m-HMPAO SPECT imaging of cerebral blood flow during REM sleep in narcoleptics. J Nucl Med 36(7):1150–1155 PubMed PMID: 7790937. eng
188. Joo EY, Tae WS, Kim JH, Kim BT, Hong SB (2004) Glucose hypometabolism of hypothalamus and thalamus in narcolepsy. Ann Neurol. 56(3):437–440 PubMed PMID: 15349874
189. Dauvilliers Y, Comte F, Bayard S, Carlander B, Zanca M, Touchon J (2010) A brain PET study in patients with narcolepsy-cataplexy. J Neurol Neurosurg Psychiatry 81 (3):344–348 PubMed PMID: 19850578. Epub 2009/10/24. eng
190. Yeon Joo E, Hong SB, Tae WS, Kim JH, Han SJ, Cho YW et al (2005) Cerebral perfusion abnormality in narcolepsy with cataplexy. Neuroimage 28(2):410–416 PubMed PMID: 16098766
191. Hong SB, Tae WS, Joo EY (2006) Cerebral perfusion changes during cataplexy in narcolepsy patients. Neurology 66(11):1747–1749 PubMed PMID: 16769955
192. Chabas D, Habert MO, Maksud P, Tourbah A, Minz M, Willer JC et al (2007) Functional imaging of cataplexy during status cataplecticus. Sleep 30(2):153–156 PubMed PMID: 17326540. eng
193. Schwartz S, Ponz A, Poryazova R, Werth E, Boesiger P, Khatami R et al (2008) Abnormal activity in hypothalamus and amygdala during humour processing in human narcolepsy with cataplexy. Brain J Neurol 131(Pt 2):514–522
194. Reiss AL, Hoeft F, Tenforde AS, Chen W, Mobbs D, Mignot EJ (2008) Anomalous hypothalamic responses to humor in cataplexy. PLoS ONE 3(5):e2225 PubMed PMID: 18493621. eng

195. Ponz A, Khatami R, Poryazova R, Werth E, Boesiger P, Schwartz S et al (2010) Reduced amygdala activity during aversive conditioning in human narcolepsy. Ann Neurol 67 (3):394–398 PubMed PMID: 20373351. Epub 2010/04/08. eng
196. Ponz A, Khatami R, Poryazova R, Werth E, Boesiger P, Bassetti CL et al (2010) Abnormal activity in reward brain circuits in human narcolepsy with cataplexy. Ann Neuroll 67 (2):190–200 PubMed PMID: 20225193. Epub 2010/03/13. eng
197. Hobson JA, McCarley RW, Wyzinski PW (1975) Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189(4196):55–58 PubMed PMID: 1094539
198. Sudo Y, Suhara T, Honda Y, Nakajima T, Okubo Y, Suzuki K et al (1998) Muscarinic cholinergic receptors in human narcolepsy: a PET study. Neurology 51(5):1297–1302 PubMed PMID: 9818849
199. Aldrich MS, Hollingsworth Z, Penney JB (1992) Dopamine-receptor autoradiography of human narcoleptic brain. Neurology 42(2):410–415 PubMed PMID: 1736175
200. Kish SJ, Mamelak M, Slimovitch C, Dixon LM, Lewis A, Shannak K et al (1992) Brain neurotransmitter changes in human narcolepsy. Neurology 42(1):229–234 PubMed PMID: 1370862
201. Eisensehr I, Linke R, Tatsch K, von Lindeiner H, Kharraz B, Gildehaus FJ et al (2003) Alteration of the striatal dopaminergic system in human narcolepsy. Neurology 60(11):1817–1819 PubMed PMID: 12796537
202. Rinne JO, Hublin C, Partinen M, Ruottinen H, Ruotsalainen U, Nagren K et al (1995) Positron emission tomography study of human narcolepsy: no increase in striatal dopamine D2 receptors. Neurology 45(9):1735–1738 PubMed PMID: 7675236
203. Rinne JO, Hublin C, Partinen M, Ruottinen H, Nagren K, Lehikoinen P et al (1996) Striatal dopamine D1 receptors in narcolepsy: a PET study with [11C]NNC 756. J Sleep Res 5 (4):262–264 PubMed PMID: 9065878
204. MacFarlane JG, List SJ, Moldofsky H, Firnau G, Chen JJ, Szechtman H et al (1997) Dopamine D2 receptors quantified in vivo in human narcolepsy. Biol Psychiatry 41(3):305–310 PubMed PMID: 9024953. eng
205. Hublin C, Launes J, Nikkinen P, Partinen M (1994) Dopamine D2-receptors in human narcolepsy: a SPECT study with 123I-IBZM. Acta Neurol Scand 90(3):186–189 PubMed PMID: 7847059
206. Staedt J, Stoppe G, Kogler A, Riemann H, Hajak G, Rodenbeck A et al (1996) [123I]IBZM SPET analysis of dopamine D2 receptor occupancy in narcoleptic patients in the course of treatment. Biol Psychiatry 39(2):107–111 PubMed PMID: 8717608
207. Khan N, Antonini A, Parkes D, Dahlitz MJ, Meier-Ewert K, Weindl A et al (1994) Striatal dopamine D2 receptors in patients with narcolepsy measured with PET and 11C-raclopride. Neurology 44(11):2102–2104 PubMed PMID: 7969966
208. Howard RJ, Ellis C, Bullmore ET, Brammer M, Mellers JD, Woodruff PW et al (1996) Functional echoplanar brain imaging correlates of amphetamine administration to normal subjects and subjects with the narcoleptic syndrome. Magn Reson Imaging 14 (9):1013–1016 PubMed PMID: 9070991
209. Ellis CM, Monk C, Simmons A, Lemmens G, Williams SC, Brammer M et al (1999) Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Actions of modafinil. J Sleep Res 8(2):85–93 PubMed PMID: 10389090
210. Thomas RJ, Kwong K (2006) Modafinil activates cortical and subcortical sites in the sleep-deprived state. Sleep 29(11):1471–1481 PubMed PMID: 17162995. eng
211. Joo EY, Seo DW, Tae WS, Hong SB (2008) Effect of modafinil on cerebral blood flow in narcolepsy patients. Sleep 31(6):868–873 PubMed PMID: 18548832. eng
212. Kim YK, Yoon IY, Shin YK, Cho SS, Kim SE (2007) Modafinil-induced hippocampal activation in narcolepsy. Neurosci Lett 422(2):91–96 PubMed PMID: 17600622. eng
213. Nose I, Ookawa T, Tanaka J, Yamamoto T, Uchimura N, Maeda H et al (2002) Decreased blood flow of the left thalamus during somnolent episodes in a case of recurrent hypersomnia. Psychiatry Clin Neurosci 56(3):277–278 PubMed PMID: 12047594
214. Eisensehr I, Noachtar S, von Schlippenbach C, Uttner I, Kleine J, Seelos K et al (2003) Hypersomnia associated with bilateral posterior hypothalamic lesion. A polysomnographic case study. Eur Neurol 49(3):169–172 PubMed PMID: 12646762
215. Arii J, Kanbayashi T, Tanabe Y, Ono J, Nishino S, Kohno Y (2001) A hypersomnolent girl with decreased CSF hypocretin level after removal of a hypothalamic tumor. Neurology 56 (12):1775–1776 PubMed PMID: 11425955
216. Arnulf I, Rico T, Mignot E (2012) Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol 11(10):918–928
217. Huang Y-S, Guilleminault C, Lin K-L, Hwang F-M, Liu F-Y, Kung Y-P (2012) Relationship between Kleine-Levin syndrome and upper respiratory infection in Taiwan. Sleep 35(1):123–129
218. Huang Y-SSG, Christian; Kao, Pan-Fu F; Liu, Feng-Yuan Y (2005) SPECT findings in the Kleine-Levin syndrome. Sleep 28 (8):955–960
219. Poryazova R, Schnepf B, Boesiger P, Bassetti C (2007) Magnetic resonance spectroscopy in a patient with Kleine-Levin syndrome. J Neurol 254(10):1445–1446
220. Hong SB, Joo, EY, Tae WS (2006) Episodiv diencephalic hypoperfusion in Kleine-Levin syndrome. Sleep 29:1091–1093
221. Billings ME, Watson NF, Keogh BP (2011) Dynamic fMRI changes in Kleine-Levin syndrome. Sleep Med. 12(5):532
222. Lu ML, Liu HC, Chen CH, Sung SM (2000) Kleine-Levin syndrome and psychosis: observation from an unusual case. Neuropsychiatry Neuropsychol Behav Neurol 13(2):140–142 PubMed PMID: 10780633
223. Landtblom AM, Dige N, Schwerdt K, Safstrom P, Granerus G (2002) A case of Kleine-Levin syndrome examined with SPECT and neuropsychological testing. Acta Neurol Scand 105(4):318–321 PubMed PMID: 11939946
224. Arias M, Crespo Iglesias JM, Perez J, Requena- Caballero I, Sesar-Ignacio A, Peleteiro-Fernandez M (2002) Kleine-Levin syndrome: contribution of brain SPECT in diagnosis. Rev Neurol 35(6):531–533 PubMed PMID: 12389171 (Sindrome de Kleine-Levin: aportacion diagnostica de la SPECT cerebral)
225. Portilla P, Durand E, Chalvon A, Habert M, Navelet Y, Prigent A et al (2002) SPECT-identified hypoperfusion of the left temporomesial structures in a Kleine-Levin syndrome. Rev Neurol (Paris) 158(5 Pt 1):593–595 PubMed PMID: 12072828 (Hypoperfusion temporomesiale gauche en TEMP dans un syndrome de Kleine-Levin)
226. Hsieh CF, Lai CL, Lan SH, Liu CK, Hsu CY (2010) Modafinil-associated vivid visual hallucination in a patient with Kleine-Levin syndrome: case report. J Clin Psychopharmacol 30 (3):347–350 PubMed PMID: 20473083
227. Young T, Peppard PE, Gottlieb DJ (2002) Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 165(9):1217–1239 PubMed PMID: 11991871
228. Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A et al (2011) Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med 183(10):1419–1426 PubMed PMID: 21037021. Epub 2010/11/03. eng

229. Arens R, Marcus CL (2004) Pathophysiology of upper airway obstruction: a developmental perspective. Sleep 27(5):997–1019 PubMed PMID: 15453561
230. Caples SM, Gami AS, Somers VK (2005) Obstructive sleep apnea. Ann Intern Med 142(3):187–197 PubMed PMID: 15684207
231. Mateika JH, Ellythy M (2003) Chemoreflex control of ventilation is altered during wakefulness in humans with OSA. Respir Physiol Neurobiol 138(1):45–57 PubMed PMID: 14519377
232. Henderson LA, Woo MA, Macey PM, Macey KE, Frysinger RC, Alger JR et al (2003) Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. J Appl Physiol 94(3):1063–1074 PubMed PMID: 12433858
233. Macey PM, Macey KE, Henderson LA, Alger JR, Frysinger RC, Woo MA et al (2003) Functional magnetic resonance imaging responses to expiratory loading in obstructive sleep apnea. Respir Physiol Neurobiol 138(2–3):275–290 PubMed PMID: 14609516
234. Harper RM, Macey PM, Henderson LA, Woo MA, Macey KE, Frysinger RC et al (2003) fMRI responses to cold pressor challenges in control and obstructive sleep apnea subjects. J Appl Physiol 94(4):1583–1595 PubMed PMID: 12514164
235. Hashimoto K, Ono T, Honda E, Maeda K, Shinagawa H, Tsuiki S et al (2006) Effects of mandibular advancement on brain activation during inspiratory loading in healthy subjects: a functional magnetic resonance imaging study. J Appl Physiol 100(2):579–586 PubMed PMID: 16195387
236. Berry DT, Webb WB, Block AJ, Bauer RM, Switzer DA (1986) Nocturnal hypoxia and neuropsychological variables. J Clin Exp Neuropsychol 8(3):229–238 PubMed PMID: 3722349
237. Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J (1991) Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol 13(6):950–964 PubMed PMID: 1779033
238. Bonnet MH (1993) Cognitive effects of sleep and sleep fragmentation. Sleep 16(8 Suppl):S65–S67 PubMed PMID: 8178030
239. Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ (1992) Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 152(3):538–541 PubMed PMID: 1546916
240. George CF, Boudreau AC, Smiley A (1996) Simulated driving performance in patients with obstructive sleep apnea. Am J Respir Crit Care Med 154(1):175–181 PubMed PMID: 8680676
241. Findley L, Unverzagt M, Guchu R, Fabrizio M, Buckner J, Suratt P (1995) Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. Chest 108(3):619–624 PubMed PMID: 7656606
242. Findley LJ, Barth JT, Powers DC, Wilhoit SC, Boyd DG, Suratt PM (1986) Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. Chest 90 (5):686–690 PubMed PMID: 3769569
243. Young T, Blustein J, Finn L, Palta M (1997) Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep 20(8):608–613 PubMed PMID: 9351127
244. Naegele B, Thouvard V, Pepin JL, Levy P, Bonnet C, Perret JE et al (1995) Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 18(1):43–52 PubMed PMID: 7761742
245. Feuerstein C, Naegele B, Pepin JL, Levy P (1997) Frontal lobe-related cognitive functions in patients with sleep apnea syndrome before and after treatment. Acta Neurol Belg 97(2):96–107 PubMed PMID: 9246377
246. Greenberg GD, Watson RK, Deptula D (1987) Neuropsychological dysfunction in sleep apnea. Sleep 10(3):254–262 PubMed PMID: 3629088
247. Harrison Y, Horne JA, Rothwell A (2000) Prefrontal neuropsychological effects of sleep deprivation in young adults—a model for healthy aging? Sleep 23(8):1067–1073 PubMed PMID: 11145321
248. Kotterba S, Rasche K, Widdig W, Duscha C, Blombach S, Schultze-Werninghaus G et al (1998) Neuropsychological investigations and event-related potentials in obstructive sleep apnea syndrome before and during CPAP-therapy. J Neurol Sci 159 (1):45–50 PubMed PMID: 9700702
249. Beebe DW, Groesz L, Wells C, Nichols A, McGee K (2003) The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 26(3):298–307 PubMed PMID: 12749549
250. Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK (2005) Functional imaging of working memory in obstructive sleep-disordered breathing. J Appl Physiol 98(6):2226–2234 PubMed PMID: 15677733
251. Zhang X, Ma L, Li S, Wang Y, Wang L (2011) A functional MRI evaluation of frontal dysfunction in patients with severe obstructive sleep apnea. Sleep Med 12(4):335–340 PubMed PMID: 21398177
252. Prilipko O, Huynh N, Schwartz S, Tantrakul V, Kim JH, Peralta AR et al (2011) Task positive and default mode networks during a parametric working memory task in obstructive sleep apnea patients and healthy controls. Sleep 34(3):293–301A PubMed PMID: 21358846. Pubmed Central PMCID: 3041705
253. Ayalon L, Ancoli-Israel S, Aka AA, McKenna BS, Drummond SP (2009) Relationship between obstructive sleep apnea severity and brain activation during a sustained attention task. Sleep 32 (3):373–381 PubMed PMID: 19294957. Pubmed Central PMCID: 2647791
254. Ayalon L, Ancoli-Israel S, Drummond SP (2009) Altered brain activation during response inhibition in obstructive sleep apnea. J Sleep Res 18(2):204–208 PubMed PMID: 19302344. Pubmed Central PMCID: 2770011
255. Ayalon L, Ancoli-Israel S, Klemfuss Z, Shalauta MD, Drummond SP (2006) Increased brain activation during verbal learning in obstructive sleep apnea. Neuroimage. 31(4):1817–1825 PubMed PMID: 16626972
256. Archbold KH, Borghesani PR, Mahurin RK, Kapur VK, Landis CA (2009) Neural activation patterns during working memory tasks and OSA disease severity: preliminary findings. J Clin Sleep Med JCSM Official Publ Am Acad Sleep Med 5(1):21–27 PubMed PMID: 19317377. Pubmed Central PMCID: 2637162
257. Castronovo V, Canessa N, Strambi LF, Aloia MS, Consonni M, Marelli S et al (2009) Brain activation changes before and after PAP treatment in obstructive sleep apnea. Sleep 32(9):1161–1172 PubMed PMID: 19750921. Pubmed Central PMCID: 2737574
258. Zhang Q, Wang D, Qin W, Li Q, Chen B, Zhang Y et al (2013) Altered resting-state brain activity in obstructive sleep apnea. Sleep 36(5):651–659 PubMed PMID: 23633747. Pubmed Central PMCID: 3624819
259. Santarnecchi E, Sicilia I, Richiardi J, Vatti G, Polizzotto NR, Marino D et al (2013) Altered cortical and subcortical local coherence in obstructive sleep apnea: a functional magnetic resonance imaging study. J Sleep Res 22(3):337–347
260. Prilipko O, Huynh N, Schwartz S, Tantrakul V, Kushida C, Paiva T et al (2012) The effects of CPAP treatment on task positive and default mode networks in obstructive sleep apnea patients: an fMRI study. PLoS ONE. 7(12):e47433 PubMed PMID: 23227139. Pubmed Central PMCID: 3515559
261. Joo EY, Tae WS, Han SJ, Cho JW, Hong SB (2007) Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. Sleep 30(11):1515–1520 PubMed PMID: 18041484. Pubmed Central PMCID: 2082095

262. Yaouhi K, Bertran F, Clochon P, Mezenge F, Denise P, Foret J et al (2009) A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 18(1):36–48 PubMed PMID: 19250174
263. Ficker JH, Feistel H, Moller C, Merkl M, Dertinger S, Siegfried W et al (1997) Changes in regional CNS perfusion in obstructive sleep apnea syndrome: initial SPECT studies with injected nocturnal 99mTc-HMPAO. Pneumologie 51(9):926–930 PubMed PMID: 9411446. Veranderungen der regionalen ZNS-Perfusion beim obstruktiven Schlafapnoe-Syndrom: Erste SPECT-Untersuchungen mit nachtlich injiziertem 99mTc-HMPAO
264. Macey PM, Henderson LA, Macey KE, Alger JR, Frysinger RC, Woo MA et al (2002) Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 166 (10):1382–1387 PubMed PMID: 12421746
265. Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR (2003) Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 4(5):451–454 PubMed PMID: 14592287
266. Gale SD, Hopkins RO (2004) Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. J Int Neuropsychol Soc 10(1):60–71 PubMed PMID: 14751008
267. Torelli F, Moscufo N, Garreffa G, Placidi F, Romigi A, Zannino S et al (2011) Cognitive profile and brain morphological changes in obstructive sleep apnea. Neuroimage 54(2):787–793 PubMed PMID: 20888921
268. Dusak A, Ursavas A, Hakyemez B, Gokalp G, Taskapilioglu O, Parlak M (2013) Correlation between hippocampal volume and excessive daytime sleepiness in obstructive sleep apnea syndrome. Eur Rev Med Pharmacol Sci 17(9):1198–1204 PubMed PMID: 23690189
269. Macey PM, Kumar R, Yan-Go FL, Woo MA, Harper RM (2012) Sex differences in white matter alterations accompanying obstructive sleep apnea. Sleep 35(12):1603–1613 PubMed PMID: 23204603. Pubmed Central PMCID: 3490353
270. Cross RL, Kumar R, Macey PM, Doering LV, Alger JR, Yan-Go FL et al (2008) Neural alterations and depressive symptoms in obstructive sleep apnea patients. Sleep 31(8):1103–1109 PubMed PMID: 18714782. Pubmed Central PMCID: 2542956
271. Kamba M, Suto Y, Ohta Y, Inoue Y, Matsuda E (1997) Cerebral metabolism in sleep apnea. Evaluation by magnetic resonance spectroscopy. Am J Respir Crit Care Med 156(1):296–298 PubMed PMID: 9230764
272. Sarchielli P, Presciutti O, Alberti A, Tarducci R, Gobbi G, Galletti F et al (2008) A 1H magnetic resonance spectroscopy study in patients with obstructive sleep apnea. Eur J Neurol Official J Eur Fed Neurol Soc 15(10):1058–1064 PubMed PMID: 18717729
273. Algin O, Gokalp G, Ocakoglu G, Ursavas A, Taskapilioglu O, Hakyemez B (2012) Neurochemical-structural changes evaluation of brain in patients with obstructive sleep apnea syndrome. Eur J Radiol 81(3):491–495 PubMed PMID: 21300501
274. O'Donoghue FJ, Wellard RM, Rochford PD, Dawson A, Barnes M, Ruehland WR et al (2012) Magnetic resonance spectroscopy and neurocognitive dysfunction in obstructive sleep apnea before and after CPAP treatment. Sleep 35(1):41–48 PubMed PMID: 22215917. Pubmed Central PMCID: 3242686
275. Alchanatis M, Deligiorgis N, Zias N, Amfilochiou A, Gotsis E, Karakatsani A et al (2004) Frontal brain lobe impairment in obstructive sleep apnoea: a proton MR spectroscopy study. Eur Respir J 24(6):980–986 PubMed PMID: 15572542
276. Alkan A, Sharifov R, Akkoyunlu ME, Kilicarslan R, Toprak H, Aralasmak A et al (2013) MR spectroscopy features of brain in patients with mild and severe obstructive sleep apnea syndrome. Clin Imaging 37(6):989–992 PubMed PMID: 23993754
277. Bartlett DJ, Rae C, Thompson CH, Byth K, Joffe DA, Enright T et al (2004) Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. Sleep Med 5 (6):593–596 PubMed PMID: 15511707
278. Halbower AC, Degaonkar M, Barker PB, Earley CJ, Marcus CL, Smith PL et al (2006) Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med 3(8):e301 PubMed PMID: 16933960. Pubmed Central PMCID: 1551912
279. Tonon C, Vetrugno R, Lodi R, Gallassi R, Provini F, Iotti S et al (2007) Proton magnetic resonance spectroscopy study of brain metabolism in obstructive sleep apnoea syndrome before and after continuous positive airway pressure treatment. Sleep 30 (3):305–311 PubMed PMID: 17425226
280. Dang-Vu TT (2013) Structural brain modifications in primary insomnia: myth or reality? Sleep 36(7):965–966 PubMed PMID: 23814328. Pubmed Central PMCID: 3669079
281. Naegele B, Pepin JL, Levy P, Bonnet C, Pellat J, Feuerstein C (1998) Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 21(4):392–397 PubMed PMID: 9646384
282. Bedard MA, Montplaisir J, Malo J, Richer F, Rouleau I (1993) Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 15(2):330–341 PubMed PMID: 8491855
283. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4(2):101–119
284. AASM (2005) International classification of sleep disorders, 2nd edn. Diagnostic and coding manual. American Academy of Sleep Medicine, Westchester
285. Pennestri MH, Whittom S, Adam B, Petit D, Carrier J, Montplaisir J (2006) PLMS and PLMW in healthy subjects as a function of age: prevalence and interval distribution. Sleep 29 (9):1183–1187 PubMed PMID: 17040005. Epub 2006/10/17. eng
286. Trenkwalder C, Walters AS, Hening WA, Chokroverty S, Antonini A, Dhawan V et al (1999) Positron emission tomographic studies in restless legs syndrome. Mov Disord 14(1):141–145 PubMed PMID: 9918358. Epub 1999/01/26. eng
287. Bucher SF, Seelos KC, Oertel WH, Reiser M, Trenkwalder C (1997) Cerebral generators involved in the pathogenesis of the restless legs syndrome. Ann Neurol. 41(5):639–645 PubMed PMID: 9153526
288. Spiegelhalder K, Feige B, Paul D, Riemann D, van Elst LT, Seifritz E et al (2008) Cerebral correlates of muscle tone fluctuations in restless legs syndrome: a pilot study with combined functional magnetic resonance imaging and anterior tibial muscle electromyography. Sleep Med 9(2):177–183 PubMed PMID: 17638594. Epub 2007/07/20. eng
289. Wetter TC, Pollmacher T (1997) Restless legs and periodic leg movements in sleep syndromes. J Neurol 244(4 Suppl 1):S37–S45 PubMed PMID: 9112588
290. Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS et al (2008) Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord 23(16):2267–2302 PubMed PMID: 18925578. Epub 2008/10/18. eng
291. Brodeur C, Montplaisir J, Godbout R, Marinier R (1988) Treatment of restless legs syndrome and periodic movements

during sleep with L-dopa: a double-blind, controlled study. Neurology 38(12):1845–1848 PubMed PMID: 3057399
292. Montplaisir J, Denesle R, Petit D (2000) Pramipexole in the treatment of restless legs syndrome: a follow-up study. European journal of neurology: the official journal of the European Federation of Neurological Societies. 7(Suppl 1):27–31 PubMed PMID: 11054156
293. Montplaisir J, Lorrain D, Godbout R (1991) Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanism. Eur Neurol 31(1):41–43 PubMed PMID: 2015836
294. Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas R, Brasic J et al (2011) The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. Sleep 34(3):341–347 PubMed PMID: 21358851. Pubmed Central PMCID: 3041710. Epub 2011/03/02. eng
295. Turjanski N, Lees AJ, Brooks DJ (1999) Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 52(5):932–937 PubMed PMID: 10102408
296. Ruottinen HM, Partinen M, Hublin C, Bergman J, Haaparanta M, Solin O et al (2000) An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. Neurology 54(2):502–504 PubMed PMID: 10668725
297. Trenkwalder C, Hening WA, Walters AS, Campbell SS, Rahman K, Chokroverty S (1999) Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. Mov Disord 14(1):102–110 PubMed PMID: 9918351. Epub 1999/01/26. eng
298. Michaud M, Soucy JP, Chabli A, Lavigne G, Montplaisir J (2002) SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J Neurol 249(2):164–170 PubMed PMID: 11985381
299. Mrowka M, Jobges M, Berding G, Schimke N, Shing M, Odin P (2005) Computerized movement analysis and beta-CIT-SPECT in patients with restless legs syndrome. J Neural Transm 112 (5):693–701 PubMed PMID: 15517434. Epub 2004/11/02. eng
300. Eisensehr I, Wetter TC, Linke R, Noachtar S, von Lindeiner H, Gildehaus FJ et al (2001) Normal IPT and IBZM SPECT in drug-naive and levodopa-treated idiopathic restless legs syndrome. Neurology 57(7):1307–1309 PubMed PMID: 11591854
301. Linke R, Eisensehr I, Wetter TC, Gildehaus FJ, Popperl G, Trenkwalder C et al (2004) Presynaptic dopaminergic function in patients with restless legs syndrome: are there common features with early Parkinson's disease? Mov Disord 19(10):1158–1162 PubMed PMID: 15390076
302. Kim KW, Jhoo JH, Lee SB, Lee SD, Kim TH, Kim SE et al (2012) Increased striatal dopamine transporter density in moderately severe old restless legs syndrome patients. Eur J Neurol Official J Eur Fed Neurol Soc 19(9):1213–1218 PubMed PMID: 22435397
303. Tribl GG, Asenbaum S, Klosch G, Mayer K, Bonelli RM, Auff E et al (2002) Normal IPT and IBZM SPECT in drug naive and levodopa-treated idiopathic restless legs syndrome. Neurology 59 (4):649–650 PubMed PMID: 12196677
304. Tribl GG, Asenbaum S, Happe S, Bonelli RM, Zeitlhofer J, Auff E (2004) Normal striatal D2 receptor binding in idiopathic restless legs syndrome with periodic leg movements in sleep. Nucl Med Commun 25(1):55–60 PubMed PMID: 15061265
305. Staedt J, Stoppe G, Kogler A, Riemann H, Hajak G, Munz DL et al (1995) Single photon emission tomography (SPET) imaging of dopamine D2 receptors in the course of dopamine replacement therapy in patients with nocturnal myoclonus syndrome (NMS). J Neural Transm Gen Sect 99(1–3):187–193 PubMed PMID: 8579804. Epub 1995/01/01. eng
306. Staedt J, Stoppe G, Kogler A, Riemann H, Hajak G, Munz DL et al (1995) Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alteration. Eur Arch Psychiatry Clin Neurosci 245(1):8–10 PubMed PMID: 7786913. Epub 1995/01/01. eng
307. Staedt J, Stoppe G, Kogler A, Munz D, Riemann H, Emrich D et al (1993) Dopamine D2 receptor alteration in patients with periodic movements in sleep (nocturnal myoclonus). J Neural Transm Gen Sect 93(1):71–74 PubMed PMID: 8103994. Epub 1993/01/01. eng
308. Happe S, Pirker W, Klosch G, Sauter C, Zeitlhofer J (2003) Periodic leg movements in patients with Parkinson's disease are associated with reduced striatal dopamine transporter binding. J Neurol 250(1):83–86 PubMed PMID: 12527997. Epub 2003/01/16. eng
309. Cervenka S, Palhagen SE, Comley RA, Panagiotidis G, Cselenyi Z, Matthews JC et al (2006) Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. Brain 129(Pt 8):2017–2028 PubMed PMID: 16816393. Epub 2006/07/04. eng
310. Stanwood GD, Lucki I, McGonigle P (2000) Differential regulation of dopamine D2 and D3 receptors by chronic drug treatments. J Pharmacol Exp Ther 295(3):1232–1240 PubMed PMID: 11082460. Epub 2000/11/18. eng
311. Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas RE, Brasic JR et al (2013) Increased synaptic dopamine in the putamen in restless legs syndrome. Sleep 36(1):51–57 PubMed PMID: 23288971. Pubmed Central PMCID: 3524542
312. Allen R (2004) Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med 5(4):385–391 PubMed PMID: 15222997. Epub 2004/06/30. eng
313. Berg D, Gerlach M, Youdim MB, Double KL, Zecca L, Riederer P et al (2001) Brain iron pathways and their relevance to Parkinson's disease. J Neurochem 79(2):225–236 PubMed PMID: 11677250
314. Berg D, Merz B, Reiners K, Naumann M, Becker G (2005) Five-year follow-up study of hyperechogenicity of the substantia nigra in Parkinson's disease. Mov Disord 20(3):383–385 PubMed PMID: 15486999
315. Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ (2001) MRI measurement of brain iron in patients with restless legs syndrome. Neurology 56(2):263–265 PubMed PMID: 11160969
316. Earley CJ, P BB, Horska A, Allen RP (2006) MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Med 7(5):458–461 PubMed PMID: 16740411. Epub 2006/06/03. eng
317. Godau J, Klose U, Di Santo A, Schweitzer K, Berg D (2008) Multiregional brain iron deficiency in restless legs syndrome. Mov Disord 23(8):1184–1187 PubMed PMID: 18442125. Epub 2008/04/30. eng
318. Godau J, Schweitzer KJ, Liepelt I, Gerloff C, Berg D (2007) Substantia nigra hypoechogenicity: definition and findings in restless legs syndrome. Mov Disord 22(2):187–192 PubMed PMID: 17133515. Epub 2006/11/30. eng
319. Schmidauer C, Sojer M, Seppi K, Stockner H, Hogl B, Biedermann B et al (2005) Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. Ann Neurol 58 (4):630–634 PubMed PMID: 16037973. Epub 2005/07/23. eng
320. Walters AS (2002) Review of receptor agonist and antagonist studies relevant to the opiate system in restless legs syndrome. Sleep Med 3(4):301–304 PubMed PMID: 14592191
321. Barriere G, Cazalets JR, Bioulac B, Tison F, Ghorayeb I (2005) The restless legs syndrome. Prog Neurobiol 77(3):139–165 PubMed PMID: 16300874. Epub 2005/11/23. eng

322. von Spiczak S, Whone AL, Hammers A, Asselin MC, Turkheimer F, Tings T et al (2005) The role of opioids in restless legs syndrome: an [11C]diprenorphine PET study. Brain 128(Pt 4):906–917 PubMed PMID: 15728657. Epub 2005/02/25. eng
323. Etgen T, Draganski B, Ilg C, Schroder M, Geisler P, Hajak G et al (2005) Bilateral thalamic gray matter changes in patients with restless legs syndrome. Neuroimage 24(4):1242–1247 PubMed PMID: 15670702
324. Unrath A, Juengling FD, Schork M, Kassubek J (2007) Cortical grey matter alterations in idiopathic restless legs syndrome: an optimized voxel-based morphometry study. Mov Disord. 2007 Sep 15;22(12):1751–1756 PubMed PMID: 17566123. Epub 2007/06/15. eng
325. Unrath A, Muller HP, Ludolph AC, Riecker A, Kassubek J (2008) Cerebral white matter alterations in idiopathic restless legs syndrome, as measured by diffusion tensor imaging. Mov Disord 23(9):1250–1255 PubMed PMID: 18464282. Epub 2008/05/09. eng
326. Celle S, Roche F, Peyron R, Faillenot I, Laurent B, Pichot V et al (2010) Lack of specific gray matter alterations in restless legs syndrome in elderly subjects. J Neurol 257(3):344–348 PubMed PMID: 19768657. Epub 2009/09/22. eng
327. Comley RA, Cervenka S, Palhagen SE, Panagiotidis G, Matthews JC, Lai RY et al (2010) A comparison of gray matter density in restless legs syndrome patients and matched controls using voxel-based morphometry. J Neuroimaging 22(1):28–32 PubMed PMID: 21091816. Epub 2010/11/26. eng
328. Hornyak M, Ahrendts JC, Spiegelhalder K, Riemann D, Voderholzer U, Feige B et al (2007) Voxel-based morphometry in unmedicated patients with restless legs syndrome. Sleep Med 9 (1):22–26 PubMed PMID: 17512782. Epub 2007/05/22. eng
329. Rizzo G, Manners D, Vetrugno R, Tonon C, Malucelli E, Plazzi G et al (2011) Combined brain voxel-based morphometry and diffusion tensor imaging study in idiopathic restless legs syndrome patients. Eur J Neurol Official J Eur Fed Neurol Soc 19 (7):1045–1049 PubMed PMID: 22175823. Epub 2011/12/20. eng
330. Rizzo G, Tonon C, Testa C, Manners D, Vetrugno R, Pizza F et al (2012) Abnormal medial thalamic metabolism in patients with idiopathic restless legs syndrome. Brain J Neurol 135(Pt 12):3712–3720
331. Allen RP, Barker PB, Horska A, Earley CJ (2013) Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. Neurology 80(22):2028–2034 PubMed PMID: 23624560. Pubmed Central PMCID: 3716406
332. Remulla A, Guilleminault C (2004) Somnambulism (sleepwalking). Expert Opin Pharmacother 5(10):2069–2074 PubMed PMID: 15461542
333. Bassetti C, Vella S, Donati F, Wielepp P, Weder B (2000) SPECT during sleepwalking. Lancet 356(9228):484–485 PubMed PMID: 10981896
334. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW (1986) Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 9(2):293–308 PubMed PMID: 3505730
335. Schenck CH, Bundlie SR, Mahowald MW (1996) Delayed emergence of a parkinsonian disorder in 38 % of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 46(2):388–393 PubMed PMID: 8614500
336. Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S et al (2002) REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59 (4):585–589 PubMed PMID: 12196654
337. Gagnon JF, Fantini ML, Bedard MA, Petit D, Carrier J, Rompre S et al (2004) Association between waking EEG slowing and REM sleep behavior disorder in PD without dementia. Neurology 62 (3):401–406 PubMed PMID: 14872020
338. Fantini ML, Ferini-Strambi L, Montplaisir J (2005) Idiopathic REM sleep behavior disorder: toward a better nosologic definition. Neurology 64(5):780–786 PubMed PMID: 15753409
339. Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P et al (1997) REM sleep behavior disorders in multiple system atrophy. Neurology 48(4):1094–1097 PubMed PMID: 9109907
340. Gilman S, Koeppe RA, Chervin RD, Consens FB, Little R, An H et al (2003) REM sleep behavior disorder is related to striatal monoaminergic deficit in MSA. Neurology 61(1):29–34 PubMed PMID: 12847152. Epub 2003/07/09. eng
341. Sakai K, Sastre JP, Salvert D, Touret M, Tohyama M, Jouvet M (1979) Tegmentoreticular projections with special reference to the muscular atonia during paradoxical sleep in the cat: an HRP study. Brain Res 176(2):233–254 PubMed PMID: 227527
342. Mazza S, Soucy JP, Gravel P, Michaud M, Postuma R, Massicotte-Marquez J et al (2006) Assessing whole brain perfusion changes in patients with REM sleep behavior disorder. Neurology 67(9):1618–1622 PubMed PMID: 17101893
343. Vendette M, Gagnon J-F, Soucy J-P, Gosselin N, Postuma R, Tuineag M et al (2011) Brain perfusion and markers of neurodegeneration in rapid eye movement sleep behavior disorder. Mov Disord Official J Mov Disord Soc 26(9):1717–1724
344. Dang-Vu T, Gagnon J-F, Vendette M, Soucy J-P, Postuma R, Montplaisir J (2012) Hippocampal perfusion predicts impending neurodegeneration in REM sleep behavior disorder. Neurology 79(24):2302–2306
345. Hanyu H, Inoue Y, Sakurai H, Kanetaka H, Nakamura M, Miyamoto T et al (2011) Regional cerebral blood flow changes in patients with idiopathic REM sleep behavior disorder. Eur J Neurol Official J Eur Fed Neurol Soc 18(5):784–788
346. Dauvilliers Y, Yves D, Boudousq V, Vincent B, Lopez R, Regis L et al (2011) Increased perfusion in supplementary motor area during a REM sleep behaviour episode. Sleep Med 12 (5):531–532
347. Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT et al (2003) Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. Sleep 26(5):507–512 PubMed PMID: 12938802
348. Kim YK, Yoon IY, Kim JM, Jeong SH, Kim KW, Shin YK et al (2010) The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. Eur J Neurol Official J Eur Fed Neurol Soc 17(3):487–492 PubMed PMID: 19968708
349. Stiasny-Kolster K, Doerr Y, Moller JC, Hoffken H, Behr TM, Oertel WH et al (2005) Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. Brain 128(Pt 1):126–137 PubMed PMID: 15548552
350. Unger MM, Moller JC, Stiasny-Kolster K, Mankel K, Berg D, Walter U et al (2008) Assessment of idiopathic rapid-eye-movement sleep behavior disorder by transcranial sonography, olfactory function test, and FP-CIT-SPECT. Mov Disord 23(4):596–569 PubMed PMID: 18175346. Epub 2008/01/05. eng
351. Albin RL, Koeppe RA, Chervin RD, Consens FB, Wernette K, Frey KA et al (2000) Decreased striatal dopaminergic innervation

in REM sleep behavior disorder. Neurology 55(9):1410–1412 PubMed PMID: 11087796
352. Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M et al (2010) Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol 9 (11):1070–1077 PubMed PMID: 20846908. Epub 2010/09/18. eng
353. Iranzo A, Tolosa E, Gelpi E, Molinuevo J, Valldeoriola F, Serradell M et al (2013) Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurol 12(5):443–453
354. Miyamoto TOS, Miyamoto M, Hirata K, Adachi T, Hattori R, Suzuki M, Ishi K (2010) Follow-up PET studies in case of idiopathic REM sleep behavior disorder. Sleep Med 11:100–101
355. Ellmore T, Hood A, Castriotta R, Stimming E, Bick R, Schiess M (2010) Reduced volume of the putamen in REM sleep behavior disorder patients. Parkinsonism Relat Disord 16(10):645–649
356. Unger M, Belke M, Menzler K, Heverhagen J, Keil B, Stiasny-Kolster K et al (2010) Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. Sleep 33(6):767–773
357. Scherfler C, Frauscher B, Schocke M, Iranzo A, Gschliesser V, Seppi K et al (2011) White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. Ann Neurol 69(2):400–407
358. Vendette M, Montplaisir J, Gosselin N, Soucy JP, Postuma RB, Dang-Vu TT et al (2012) Brain perfusion anomalies in rapid eye movement sleep behavior disorder with mild cognitive impairment. Mov Disord Official J Mov Disord Soc 27(10):1255–1261 PubMed PMID: 22791632. Epub 2012/07/14. eng
359. Shirakawa S, Takeuchi N, Uchimura N, Ohyama T, Maeda H, Abe T et al (2002) Study of image findings in rapid eye movement sleep behavioural disorder. Psychiatry Clin Neurosci 56(3):291–292 PubMed PMID: 12047600
360. Miyamoto M, Miyamoto T, Kubo J, Yokota N, Hirata K, Sato T (2000) Brainstem function in rapid eye movement sleep behavior disorder: the evaluation of brainstem function by proton MR spectroscopy (1H-MRS). Psychiatry Clin Neurosci 54(3):350–351 PubMed PMID: 11186109. Epub 2001/02/24. eng
361. Iranzo A, Santamaria J, Pujol J, Moreno A, Deus J, Tolosa E (2002) Brainstem proton magnetic resonance spectroscopy in idopathic REM sleep behavior disorder. Sleep 25(8):867–870 PubMed PMID: 12489892
362. Hanoglu L, Ozer F, Meral H, Dincer A (2006) Brainstem 1H-MR spectroscopy in patients with Parkinson's disease with REM sleep behavior disorder and IPD patients without dream enactment behavior. Clin Neurol Neurosurg 108(2):129–134 PubMed PMID: 15936138. Epub 2005/06/07. eng