Sleep Disorders

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Contents

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Abstract

Sleep disorders have been the subject of a number of positron emission tomography and single-photon emission computed tomography studies. Narcoleptic patients with cataplexy displayed decreased hypothalamic and thalamic perfusion during resting wakefulness, which may be related to hypocretinergic deficiency and altered vigilance. However, nuclear imaging data on narcolepsy without cataplexy and idiopathic hypersomnia remain scarce. In restless legs syndrome and periodic limb movements, hypoactivity in pre- and postsynaptic dopaminergic transmission in the striatum and substantia nigra may underlie compulsive limb movements. Sleepwalking showed specific brain perfusion changes during slow wave sleep and wakefulness, possibly indicative of a dissociated state. Rapid eye movement sleep behavior disorder patients showed changes in blood flow in the pons, frontal lobes, striatum, and hippocampus, linking this disorder to later onset of neurodegenerative diseases (synucleinopathies). Localized brain metabolism increases during non-rapid eye movement sleep in insomnia and depression are in line with the "hyperarousal" hypothesis underlying sleep disturbances in these patients. Even with these insights, radioisotope imaging in sleep medicine is still in its infancy. Further research should aim to increase sample sizes, provide adequate control groups, and acquire additional timepoints for imaging, for instance, before, during, and after the onset of symptoms.

33.1 Introduction

The growing field of sleep medicine has seen an increase in the use of neuroimaging techniques to gain insight into the neurobiological bases of sleep disorders. Positron emission tomography (PET) is a functional brain imaging technique that requires the injection of positron-emitting isotopes into the bloodstream, in order to monitor the differential blood flow (regional cerebral blood flow, rCBF) or glucose consumption (cerebral metabolic rate for glucose, CMRglu) in metabolically active areas, or to observe the distribution of a neurotransmitter receptor ligand. Single-photon emission computed tomography (SPECT) also requires the injection of a radiolabeled compound. A gamma camera then detects the photons emitted

reflecting the distribution of the radioisotope according to the differential brain perfusion or neurotransmitter function. The use of PET and SPECT in sleep medicine has thus far been limited but is expanding rapidly.

These techniques were initially applied to the investigation of normal brain function across the sleep-wake cycle. Sleep can be separated into two stages: rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep in normal subjects exhibits sustained neural activity and cerebral blood flow (Jones 1991). Compared to wakefulness and NREM sleep, REM sleep showed increased blood flow and glucose metabolism in the amygdala, thalamus, hippocampus, anterior cingulate cortex, temporo-occipital areas, basal forebrain, and brainstem (Maquet et al. 1990). Deactivations were present in the dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex (Maquet 1997, 2000; Maquet et al. 1990). In contrast to REM sleep, NREM sleep was mainly characterized by a decrease in cerebral blood flow, predominantly in the dorsal pons, mesencephalon, thalami, basal ganglia, basal forebrain, anterior hypothalamus, medial prefrontal cortex, anterior cingulate cortex, and precuneus (Andersson et al. 1998; Braun et al. 1997; Kajimura et al. 1999; Maquet and Franck 1997; Maquet et al. 1996, 2000).

In this chapter, PET and SPECT neuroimaging studies of sleep-related disorders will be discussed, namely, narcolepsy; restless legs syndrome (RLS), often associated with periodic limb movements (PLM); parasomnias, present during either REM sleep (e.g., REM sleep behavior disorder, RBD) or during NREM sleep (e.g., sleepwalking); and finally insomnia, often associated with depression. It is important to understand the differential limitations of PET and SPECT measures in imaging paroxysmal disorders such as disorders of sleep. Whereas metabolic measures (e.g., CMRglu, FDG PET) are suited to observing temporal changes between sleep states, measures of neurotransmission (e.g., dopamine) offer information about the integrity of these pathways, less likely to show variability across sleep state transitions. Other neuroimaging techniques were also used in sleep research and sleep medicine and included anatomical studies with magnetic resonance imaging (MRI) and functional brain responses with functional MRI (fMRI). Such studies exceed the scope of the present chapter and are reviewed elsewhere (Cross and Dang-Vu 2019; Dang-Vu et al. 2007, 2009; O'Byrne et al. 2014).

33.2 Central Hypersomnolence Disorders

Excessive daytime sleepiness, defined as episodes of irrepressible need to sleep during daytime, is a common experience that can be caused by several medical conditions, substance abuse, and more generally insufficient and/or disturbed sleep (Ohayon 2008). However, when not attributable to these conditions or to another sleep disorder such as sleep apnea, excessive daytime sleepiness is the main symptom of central hypersomnolence disorders (ICSD-3), (Sateia 2014) which include narcolepsy and idiopathic hypersomnia (IH). With an estimated prevalence of 0.03% (for narcolepsy) and 0.5% (for IH) (Hale et al. 2016), these

disabling neurological conditions can have severe complications ranging from increased risk of accidents to cognitive impairment and depression, leading to a poor quality of life (Ozaki et al. 2008).

33.2.1 Narcolepsy

Besides excessive daytime sleepiness, other frequent symptoms of narcolepsy include sleep paralysis, hypnagogic hallucinations, and sleep fragmentation, with frequent nighttime awakenings. Their sleep periods are also characterized by a premature entry into REM sleep (sleep-onset REM periods, SOREMPs). A common but unspecific biological marker that is found in narcolepsy is the human leukocyte antigen (HLA) subtype DQB1*0602. Narcolepsy is divided in two subtypes depending on the presence or not of cataplexy, which is defined by the sudden (partial or complete) loss of muscle tone triggered by emotional stimulation (Dauvilliers et al. 2014). Approximately 70% of patients with narcolepsy are diagnosed with *narcolepsy type 1* (*NT1*; previously called narcolepsy-cataplexy) characterized by a reduction in cerebral spinal fluid (CSF) hypocretin-1 levels (Thannickal et al. 2000). This deficit is thought to be caused by an autoimmune component damaging hypocretin (also termed orexin)-producing neurons in the lateral hypothalamus, which would produce these cataplexy attacks (Liblau et al. 2015). Hypocretinergic dysfunction is thought to underlie the unstable sleep-wake transitions and impaired vigilance in NT1 (Dauvilliers et al. 2007). Narcolepsy patients who do not report cataplexy are grouped into the *narcolepsy type 2 (NT2)* subtype, in which there is no consistent CSF hypocretin-1 deficit (Mignot et al. 2002).

Neuroimaging techniques have been mainly applied to NT1 in order to decipher the neurobiological bases of this disorder. SPECT and PET studies looked at neuromodulatory changes (dopamine, DA; acetylcholine, ACh; serotonin, 5-HT), as well as glucose metabolism and brain perfusion, during the sleep-wake cycle. Research has proven largely inconclusive, particularly with regard to neurotransmission. However, several neuroimaging studies on NT1 have consistently demonstrated both structural and functional alterations of the hypothalamus, which is in line with the pathophysiological concept that NT1 underlies a deficiency of the hypocretin system. Moreover, several functional studies point to disturbed limbic activity, consistent with reduced vigilance, hypocretinergic dysfunction, and abnormalities in emotional processing. A summary of these findings on NT1 is provided below and in Table 33.1 and Fig. 33.1. In contrast, NT2 did not receive much attention in the brain imaging field with only one study using nuclear imaging so far (see Sect. 33.2.1.5).

Table 33.1 SPECT and PET studies in narcolepsy-cataplexy

Study	Imaging technique employed	Target	Number of patients/ controls	Patients receiving treatment/ total number of patients	Results
Sudo et al. (1998)	PET ^{11}C-MPB	ACh	11/21	0/11	No change
Derry et al. (2006)	PET ^{18}F-MPPF	5HT-1A	14/0	12/14	Inconclusive in absence of control group
Eisensehr et al. (2003a, b)	SPECT 1PT	Presynaptic DA binding	7/7	0/7	No change
Rinne et al. (2004)	PET ^{11}C-CFT	Presynaptic DA binding	10/15	0/10	No change
Eisensehr et al. (2003a, b)	SPECT IBZM	Postsynaptic DA (D2) binding	7/7	0/7	Increased striatal DA
Hublin et al. (1994)	SPECT IBZM	Postsynaptic DA (D2) binding	6/8	0/6	No change
Staedt et al. (1996)	SPECT IBZM	Postsynaptic DA (D2) binding	10/10	0/10	No change
Rinne et al. (1995)	PET ^{11}C-raclopride	Postsynaptic DA (D2) binding	7/7	6/7	No change
Khan et al. (1994)	PET ^{11}C-raclopride	Postsynaptic DA (D2) binding	17/32	12/17	No change
MacFarlane et al. (1997)	PET ^{18}F-PSP	Postsynaptic DA (D2) binding	6/6	0/6	No change
Joo et al. (2004)	PET ^{18}F-FDG	CMRglu	24/24	0/24	Reduced CMRglu in hypothalami and thalamic nuclei
Dauvilliers et al. (2010)	PET ^{18}F-FDG	CMRglu	21/21	14/21	Increase of CMRglu in limbic cortex
Joo et al. (2004)	SPECT ^{99m}Tc-ECD	rCBF	25/25	0/25	Reduced cerebral perfusion in hypothalami

(continued)

Table 33.1 (continued)

Study	Imaging technique employed	Target	Number of patients/ controls	Patients receiving treatment/ total number of patients	Results
Hong et al. (2006)	SPECT ^{99m}Tc-ECD	rCBF during a cataplectic attack	2/0	0/2	Increased perfusion in limbic areas, basal ganglia, thalami, sensorimotor cortices and brainstem. Decreased perfusion in prefrontal cortex and occipital lobe
Chabas et al. (2007)	SPECT ^{99m}Tc-ECD	rCBF during a cataplectic attack	1/0	0/1	Increased perfusion in cingulate cortex, orbitofrontal cortex, and right putamen

PET and SPECT studies in narcolepsy-cataplexy, including citation, the specific imaging technique employed, targeted physiology, the number of patients and controls, the number of participants receiving treatment out of the total number of patients, and a summary of the results

33.2.1.1 Acetylcholine, Serotonin, and Dopamine Functions in Narcolepsy

Sudo et al. (1998) focused on ACh neurotransmission in narcolepsy-cataplexy. They used PET with the radioligand ^{11}C-*N*-methyl-4-piperidyl-benzilate (^{11}C-MPB) in order to target the muscarinic ACh receptor. When comparing 11 patients with narcolepsy-cataplexy to 21 controls, there was no difference in ^{11}C-MPB binding in the thalamus, pons, striatum, or cerebral cortex.

Derry et al. (2006) evaluated 5-HT neurotransmission in patients with narcolepsy-cataplexy. They used PET with 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p*-^{18}F-fluoro-benzamidoethylpiperazine (^{18}F-MPPF) in order to study 5-HT$_{1A}$ receptors. This study found an increase in ^{18}F-MPPF binding in the anterior cingulate, temporal, and mesio-temporal cortices in patients during sleep compared to wakefulness. However, this study is limited by the lack of a control group.

A few studies investigated presynaptic DA binding in narcolepsy-cataplexy using ^{123}I-(*N*)-(3-iodopropene-2-yl)-2b-carbomethoxy-3b-(4-chlorophenyl)tropane (^{123}I-IPT) SPECT (Eisensehr et al. 2003a, b) and ^{11}C-2b-carbomethoxy-3b-(4-fluorophenyl)tropane (^{11}C-CFT) PET (Rinne et al. 2004). However, there was no significant difference when comparing patients with narcolepsy-cataplexy and controls. When looking at postsynaptic D2 receptor binding, a study found a difference between patients and controls using SPECT and ^{123}I-(*S*)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl] methyl)benzamide (^{123}I-IBZM). They found

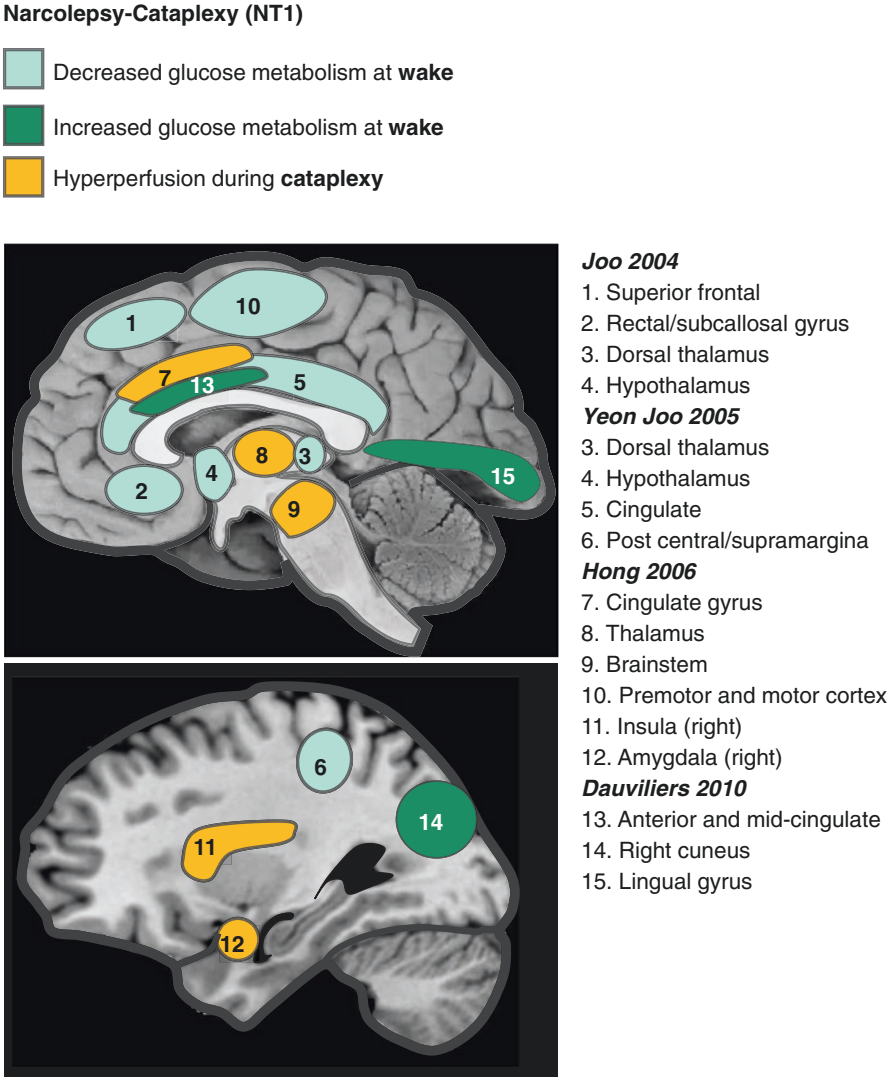


Fig. 33.1 Brain regions showing differences in CMRglu or rCBF during wakefulness in narcolepsy-cataplexy (NT1), as well as hyperperfusion (rCBF) during cataplectic attack. Adapted from Dang-Vu et al. (2014)

increased D2 binding in the striatum in seven patients with narcolepsy-cataplexy. There was also a positive correlation between IBZM binding to the striatum and the incidence of sleep attacks and cataplexy (Eisensehr et al. 2003b). However, other studies using SPECT scans with IBZM were not able to replicate these findings (Hublin et al. 1994; Staedt et al. 1996). Khan et al. (1994) and Rinne et al. (1995) examined the relationship between dopamine and narcolepsy-cataplexy using a

PET study with ^{11}C-raclopride, but their results were inconclusive. MacFarlane et al. (1997) conducted a study using PET with ^{18}F-fluoropropyl-spiperone (^{18}F-PSP) ligand and were not able to find a difference in the striatal binding of D2 in patients with narcolepsy-cataplexy.

33.2.1.2 Brain Glucose Metabolism and Perfusion in Narcoleptic Individuals

Another important aspect that several neuroimaging studies examined is the difference in narcoleptic brain activity during the day. Two studies concentrated on the assessment of CMRglu during resting wakefulness. One study assessed the CMRglu of 24 patients with narcolepsy (including 21 with cataplexy) and 24 normal individuals using PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). They found that patients had reduced CMRglu in the bilateral posterior hypothalami and mediodorsal thalamic nuclei (Joo et al. 2004). However, this study did not include EEG measurements, which weakens the strength of the findings. Another study used SPECT with Technetium-^{99}m-ethylcysteinate dimer (^{99m}Tc-ECD) and found that there was hypoperfusion in the bilateral anterior hypothalami. This study also found decreased rCBF in the caudate, superior/middle frontal gyri, postcentral gyrus, parahippocampal gyrus, and cingulate cortex in patients with narcolepsy-cataplexy (Yeon Joo et al. 2005). Both studies concluded that altered hypothalamic activity could reflect hypocretin deficiency in patients with narcolepsy-cataplexy, while the other neuroimaging patterns could be related to dysfunctions in emotional and cognitive processes. In contrast, a study conducted by Dauvilliers et al. (2010) used PET with ^{18}F-FDG and found an increase in CMRglu in the limbic cortex (more precisely in the anterior and midcingulate cortex), as well as in the right cuneus and lingual gyrus. However, this last study included patients treated with psychostimulants and did not use an objective assessment of vigilance with EEG.

33.2.1.3 Neural Correlates of Cataplexy

Given the inherent difficulty in "catching" a patient with narcolepsy in the scanner during a cataplectic episode, few studies have examined brain activity during cataplexy (loss of muscle tone). A study was conducted using ^{99m}Tc-ECD SPECT on two individuals suffering from narcolepsy with cataplexy. Scans obtained *during* a cataplexy episode were compared to those recorded during wakefulness and REM sleep. Cataplexy was associated with increased perfusion in limbic areas (amygdala, cingulate gyrus), basal ganglia, thalami, sensorimotor cortices, and the brainstem. Conversely, perfusion decreased in the prefrontal cortex and the occipital lobe (Hong et al. 2006). Increased activity in the cingulate cortex and amygdala may underlie abnormalities in the neural processing of emotions (which typically trigger cataplectic episodes), but the small sample limits the interpretation of findings. A case study using SPECT with ^{99m}Tc-ECD found an increased perfusion in the cingulate cortex and basal ganglia during an episode of cataplexy, in agreement with the previous report (Chabas et al. 2007). Dauvilliers et al. (2010) finally scanned

two patients with narcolepsy-cataplexy with PET with ^{18}F-FDG during a cataplectic attack, but did not find any significant difference when cataplexy scans were compared to the corresponding baseline wakefulness scans of the same patients.

33.2.1.4 Pharmacological Treatment of Narcolepsy

Since the main symptom of narcolepsy is excessive sleepiness, medications that promote vigilance are vital in narcolepsy treatment. Psychostimulants are known to induce enhanced wakefulness as well as improvements in physical functioning; hence this class of drugs has seen much use in treating narcolepsy. Studies involving functional neuroimaging techniques such as SPECT and PET have investigated the neural effects of these drugs in patients with narcolepsy.

Methylphenidate

Methylphenidate, an amphetamine derivative, is commonly used for treating narcolepsy. One SPECT study used ^{133}Xe inhalation to examine rCBF in patients with narcolepsy before and after treatment with methylphenidate for about 2 weeks. Administration of the drug increased rCBF during the awake state in the brainstem and cerebellar region (Meyer et al. 1980). The specificity of this finding to narcolepsy cannot be assessed, because controls were omitted in this study. Moreover, whether the patients had a history of cataplexy was not mentioned.

Modafinil

Modafinil is another psychostimulant drug used to promote wakefulness in patients with sleep disorders. In one experiment, ^{99m}Tc-ECD SPECT was performed when patients with narcolepsy-cataplexy were in the awake state, both before and after a 4-week treatment with either modafinil or a placebo (Joo et al. 2008). Modafinil caused a significant reduction in subjective daytime sleepiness, while the placebo did not, and patients in the on-modafinil condition showed an increase in rCBF in the bilateral prefrontal cortices (Joo et al. 2008). Thirty-two narcolepsy patients took part in this experiment, but in the absence of controls, the findings cannot be specifically applied to narcolepsy. Another experiment employed ^{18}F-FDG PET to measure CMRglu in patients with narcolepsy-cataplexy (Dauvilliers et al. 2010). Some of the patients were given modafinil and/or antidepressants (for treating cataplexy). Narcoleptics who received the treatment had a higher CMRglu in the cerebellum and the primary sensorimotor cortex compared to untreated patients, which contrasts with the SPECT study by Joo et al. (2008), in which modafinil was associated with a decrease in rCBF in the cerebellum. Researchers conducted another study using ^{18}F-FDG PET to assess changes in CMRglu after the administration of modafinil (Kim et al. 2007). Eight patients with narcolepsy (including six with cataplexy) completed the experiment. After 2 weeks of treatment with modafinil, the left hippocampus of narcoleptics exhibited an increase in CMRglu compared to pretreatment scans. Given that similar neuroimaging pattern was found with modafinil treatment in healthy volunteers (Joo et al. 2008), the specificity of this finding to narcolepsy might be questioned.

33.2.1.5 Narcolepsy Type 2

So far, only one study investigated NT2 using nuclear imaging. Huang et al. (2018) compared 29 patients with NT2, 26 healthy sleepers, and 104 drug-free and newly diagnosed patients with NT1 using ^{18}F-FDG PET during wakefulness. They found increased metabolic rate in the fusiform, striatum, thalamus, hippocampus, basal ganglia, and cerebellum in NT1 compared to NT2. However, hypometabolism was more prominent in patients with type 2 in the Heschl's gyrus and paracentral lobule compared to NT1. Moreover, the hypo- and hypermetabolism seen in NT1 patients compared to healthy controls were not observed in patients with NT2. They found that in both types of narcoleptic patients, the alteration in brain metabolism was correlated with performance in neurocognitive tests (i.e., Continuous Performance Test and Wisconsin Card Sorting Test). This study concluded that NT2 patients exhibit less brain metabolism alterations and less severe cognitive impairment due to preserved hypothalamus integrity (Huang et al. 2018).

33.2.1.6 Summary

Generally, SPECT and PET studies did not demonstrate a consistent difference in ACh, DA, or 5-HT neurotransmission in narcolepsy-cataplexy. Patients had reduced activity in the bilateral, hypothalamic, and thalamic nuclei, in agreement with a dysfunction of the hypocretinergic system and an impairment of vigilance. Importantly, alterations of limbic structures were found and are in agreement with abnormalities in emotional processing. Furthermore, these imaging data are in agreement with neuropsychological studies finding symptoms of narcolepsy in patients with hypothalamic lesions (Dempsey et al. 2003; Muller 2010). Although studies showed functional brain changes in narcoleptic patients posttreatment with the drugs discussed above, the meaning and significance of these differences still remain unclear, especially given the general lack of control and/or placebo groups. Further studies are thus needed to provide information on the specificity of these drug effects to patients with narcolepsy. Moreover, given the recent clinical distinction between NT1 and NT2, further investigation on the neural mechanisms distinguishing these two disorders needs to be performed.

33.2.2 Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is characterized by excessive daytime sleepiness but, in contrast to narcolepsy, does not involve cataplexy, SOREM periods, or hypocretin-1 deficiency. Compared to NT1, IH has been less investigated, and the neural correlates of IH remain unclear. So far, only one study investigated IH using MRI (Pomares et al. 2019) and SPECT (Boucetta et al. 2017), and one study used PET (Dauvilliers et al. 2017). Boucetta and colleagues scanned 13 patients with IH and 16 healthy sleepers using ^{99m}Tc-ECD SPECT to assess cerebral blood flow during resting wakefulness. Patients with IH exhibited lower rCBF in the medial prefrontal and posterior cingulate cortices. The altered rCBF levels in the medial prefrontal cortex were correlated with higher self-reported daytime sleepiness (Boucetta et al. 2017). As these regions belong to the default mode network (DMN), which plays a

key role in the maintenance of conscious awareness (Greicius et al. 2003), their lower function in IH might contribute to the impaired vigilance of IH patients during the daytime. In addition, the altered rCBF in these regions was strikingly similar to the rCBF distribution found during NREM sleep in good sleepers (Dang-Vu et al. 2005) reflecting the possible intrusion of NREM sleeplike patterns into wakefulness in IH (See Fig. 33.2).

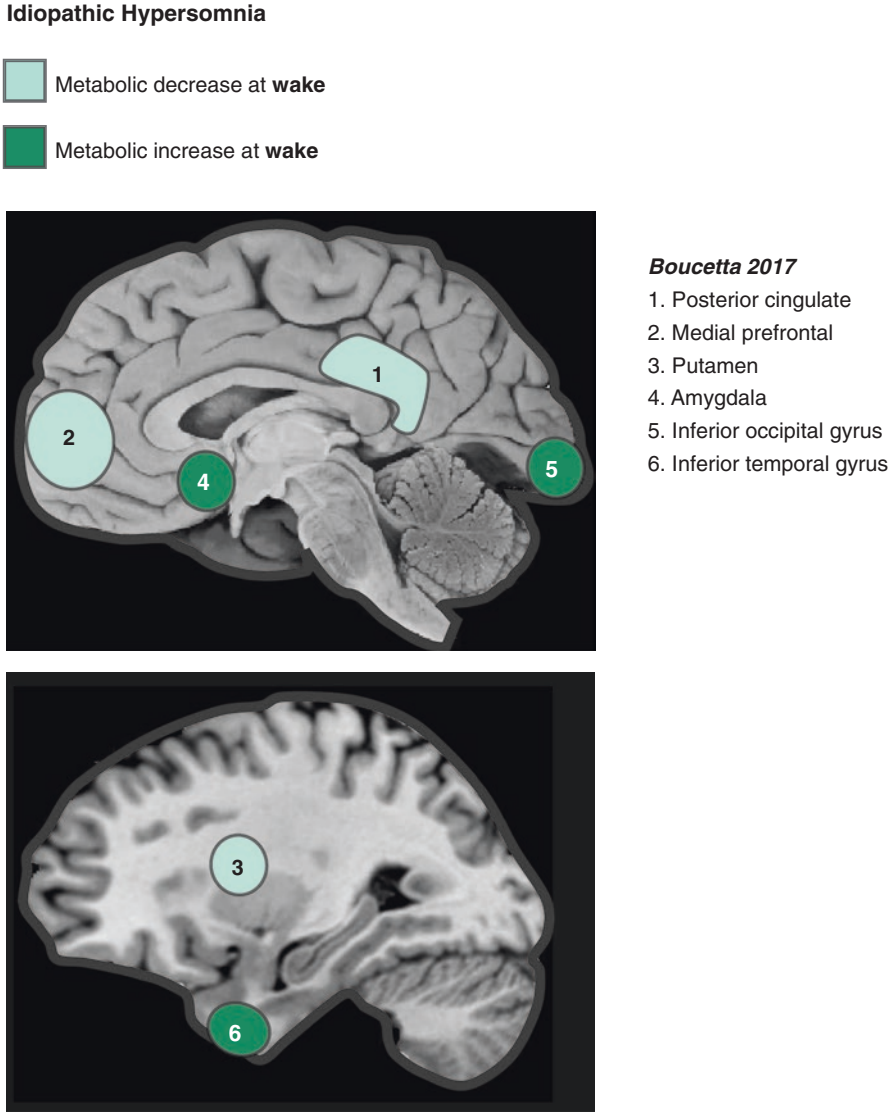


Fig. 33.2 Brain regions showing hyperperfusion or hypoperfusion in rCBF during wake in patients with idiopathic hypersomnia (IH). The rCBF decrease during wake in IH is strikingly similar to the decrease in rCBF observed during NREM sleep in good sleepers (Dang-Vu et al. 2005)

In contrast, using ^{18}F-FDG PET scanner in 9 IH, 16 NT1, and 19 healthy controls during wakefulness, Dauvilliers et al. (2017) revealed no hypometabolism in both IH and NT1 patients compared to healthy controls but hypermetabolism in similar regions in both disorders, including bilateral middle cingulate and fusiform regions, the Rolandic operculum, and the temporal and insula lobes. Given the similar alterations found in IH and NT1, they suggested that their results might reflect the neural correlates of excessive daytime sleepiness rather than specific features of each disorder (Dauvilliers et al. 2017).

The difference in sample characteristics and techniques used might contribute to these divergent findings. Further investigation needs to be performed between the different types of central hypersomnolence disorders, in order to understand the common and distinct alterations underlying each disorder.

33.3 Restless Legs Syndrome and Periodic Limb Movements

Restless legs syndrome (RLS) and periodic limb movements (PLM) are distinct yet overlapping sensorimotor disorders. RLS is characterized by an overwhelming urge to move the legs (and less often, the arms), especially when at rest and in the evening or at night. The compulsion is associated with persistent feelings of discomfort from deep inside the limbs (AASM 2005; Allen et al. 2003). PLM is distinguished by intermittent episodes of repeated and highly stereotyped limb movements when at rest, typically during NREM sleep (PLMS), but also occurring during wakefulness (PLMW). The same patient can exhibit both PLMS and PLMW. The movement typically consists of an extension of the big toe and partial flexion of the ankle, knee, and, less often, hip. While these movements disturb sleep and can result in arousal or awakening, patients are mostly unaware of the movements or even that their sleep has been disturbed. Diagnosis requires a polysomnographic recording in combination with a complaint such as "unrefreshing" sleep (AASM 2005; Pennestri et al. 2006).

Epidemiological studies estimate a 5–20% prevalence of RLS (Allen et al. 2003) and a 3.9% prevalence of PLMS in the general population (Ohayon and Roth 2002). RLS-related symptoms are responsible for sleep-onset insomnia and nocturnal awakenings in 94% of patients (Montplaisir et al. 1997). RLS can occur in an isolated form (idiopathic) or can be secondary to (or associated with) other medical conditions, such as iron deficiency anemia, neuropathy, and Parkinson's disease (PD) (AASM 2005; Allen et al. 2003; Pedroso et al. 2013). Depression and anxiety-related psychiatric illnesses are more prevalent in RLS and PLM patients than in healthy individuals (Pennestri et al. 2006; Picchietti 2006).

RLS and PLM frequently co-occur. However, PLM is nonspecific, occurring in isolation in healthy individuals, or comorbid with other sleep disorders such as narcolepsy, RBD, and sleep apnea (Pennestri et al. 2006). Since both disorders are so closely associated, few neuroimaging studies have examined PLM alone, and instead RLS and PLM are most often considered in concert. The following section will first describe neuroimaging studies centered on RLS and will end by covering the few studies of PLM alone.

33.3.1 Restless Legs Syndrome

There are few functional neuroimaging studies of RLS. A PET study by Trenkwalder et al. (1999) involving six RLS patients and six age-matched controls measured CMRglu with ^{18}F-FDG and found no significant differences. It is noteworthy that the patients were scanned outside of the symptomatic period.

Most PET and SPECT studies of RLS have looked for neurotransmission abnormalities using radioligands for DA and opioids. It has been shown that DA antagonists exacerbate RLS symptoms, whereas DA agonists and opioids are the major form of therapy for RLS (Stiasny-Kolster et al. 2005; Trenkwalder et al. 2008). DA studies focused mainly on the striatum, examining both presynaptic DA transporter (DAT) and postsynaptic D2 receptor binding. Striatal DAT can be taken as an indicator of DA neuron density in the substantia nigra (SN). Some PET studies showed decreased presynaptic DA function in the striatum of RLS patients versus controls, using either 6-[^{18}F]fluoro-L-dopa (^{18}F-dopa) (Ruottinen et al. 2000; Turjanski et al. 1999) or ^{11}C-methylphenidate (Earley et al. 2011). However, an early PET study using ^{18}F-dopa found no such difference, albeit with a limited sample of patients (Trenkwalder et al. 1999). Furthermore, a number of SPECT studies found no difference in DAT in RLS versus controls, using ^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane (^{123}I-β-CIT) (Michaud et al. 2002; Mrowka et al. 2005) or ^{123}I-IPT (Eisensehr et al. 2001; Linke et al. 2004). Recently, Lin and colleagues used ^{99}mTechnetium-[2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo(3,2,1)oct-2-yl] methyl](2mercapto-ethyl)amino]ethyl]amino]ethanethiolato(3-)-N2,N2,S2,S2]oxo-[1R-(exo-exo)] (^{99}mTc-TRODAT) SPECT and revealed significant decrease in DAT striatal binding in 22 early-stage RLS patients compared to 12 healthy controls. Specifically, they showed uptake deficits in both sides of the caudate nucleus and striatum (Lin et al. 2016).

The discrepancy in these findings may be attributable to particular pharmacokinetic properties of radioligands used in PET and SPECT. Earley et al. (2011), in the aforementioned study, scanned their patients in the morning (n = 20) and evening (n = 16) and found no difference in DA according to time of day. Hence, time of day does not seem to modulate DAT binding. There was also no significant correlation between severity of RLS symptoms and DAT. Kim et al. (2012) employed SPECT with ^{123}I-β-CIT and ^{123}I-IBZM and, in contrast with all previous presynaptic DA studies, found an increase in DAT density in the striatum, as well as the caudate and posterior putamen.

Postsynaptic D2 receptor binding studies are also rather equivocal. A few SPECT studies used ^{123}I-IBZM. Most found no difference (Eisensehr et al. 2001; Tribl et al. 2002, 2004), while one found a slight decrease in striatal D2 receptor binding in RLS patients versus controls (Michaud et al. 2002). Two PET studies using ^{11}C-raclopride found divergent results: Turjanski et al. (1999) found a decrease and Cervenka et al. (2006) an increase in striatal D2 receptor binding. This discrepancy may be explained by the inclusion of a sample of RLS patients previously exposed to DA drugs in the study by Turjanski et al. (1999), whereas patients in the other study were drug-naïve

(Cervenka et al. 2006). It has in fact been shown that D2 receptors can be downregulated by chronic drug treatment, hence decreasing ligand binding (Stanwood et al. 2000). Cervenka et al. (2006) measured D2 receptor binding in extrastriatal structures by scanning 16 RLS patients with ^{11}C-FLB457 and found increased binding potential in the striatum as well as in the insula, thalamus, and anterior cingulate cortex. The areas showing increased D2 receptor binding are part of the medial nociceptive system, which regulates the affective component of pain. If this system were to undergo endogenous DA depletion, one could expect upregulation of D2 receptors, just as the study showed. The authors also took measurements in the morning and the evening and found no diurnal changes in D2 binding potential. Furthermore, no significant correlation was found between RLS symptom rating and D2 binding potential. Hence diurnal changes in RLS symptom severity cannot be accounted for by presynaptic DA transmission (Earley et al. 2011) or postsynaptic D2 binding (Cervenka et al. 2006). In a later PET study using ^{11}C-raclopride, Earley et al. (2013) found that RLS patients had lower D2 receptor binding potential in the putamen, as well as the caudate but not ventral striatum. Interestingly, in light of the divergent results of previous PET and SPECT studies, the authors of the study deemed D2 receptor binding potential of questionable value to RLS research.

Since RLS seems to be a disorder of the nociceptive system, it follows that the opioid system, which modulates pain, may play a role in RLS. Indeed, opioid receptor agonists have been shown to improve RLS symptoms (Walters 2002). This effect may however be mediated by DA and may not necessarily reflect a deficiency in endogenous opioids (Barriere et al. 2005). In support of this, one PET study has examined opioids in RLS, using ^{11}C-diprenorphine (a nonselective opioid receptor ligand), and found no differences between patients and controls, although the authors did find some correlations between RLS severity or pain scores and opioid binding in several brain areas (von Spiczak et al. 2005).

In addition to nigrostriatal abnormalities in DA neurotransmission, descending dopaminergic projections to the lower brainstem and spinal cord, as well as opioid receptors in the spinal cord, are also thought to play an important role in RLS pathophysiology. In addition, spinal cord lesions and peripheral neuropathies are associated with RLS (Trenkwalder and Paulus 2010). However, limitations in the resolution of PET and SPECT in these areas preclude further investigation using these imaging techniques.

33.3.2 Periodic Limb Movements

Dopaminergic transmission has been studied in relation to PLM. At the presynaptic level, Happe et al. (2003) measured DA transmission in 11 patients with Parkinson's disease (PD) using SPECT with ^{123}I-β-CIT. Patients with PD showed a stark reduction in striatal binding compared to controls, as expected. By also measuring PLMS by polysomnography, the authors detected a negative correlation between the number of PLMS and striatal DA binding values. This suggests a possible role of presynaptic DA deficiency in PD-induced PLMS. Staedt and colleagues examined

postsynaptic D2 receptor binding in the striatum of PLMS patients in a few studies using SPECT and ^{123}I-IBZM (Staedt et al. 1993, 1995a, b) and found decreased D2 receptor occupancy (Staedt et al. 1993, 1995a). DA replacement therapy can reverse this pattern and restore sleep quality (Staedt et al. 1995b).

33.3.3 Summary

PET and SPECT studies on RLS and PLM seem to indicate a hypoactivity of DA neurotransmission underlying these disorders, both at the presynaptic and postsynaptic levels. DA deficiency, in concert with CNS iron depletion, may unbalance the sensorimotor control of pain. Further research into RLS and PLM brain activation during sleep is needed to confirm these findings and shed further light on these little explored disorders.

33.4 Parasomnias

Parasomnias are characterized by undesirable physical events and experiences occurring during entry into sleep, within sleep, or during arousals from sleep (AASM 2005). They are divided into two categories: REM and NREM parasomnias. Although some forms are benign, others may result in injury and sleep disruption, severely affecting one's life. PET and SPECT bring important contributions to the pathophysiology of parasomnias.

33.4.1 Sleepwalking

One common type of NREM parasomnia is sleepwalking, formally known as somnambulism. It "consists of a series of complex behaviors that are usually initiated during arousals and slow wave sleep (SWS; i.e., deep NREM sleep) and culminate in walking around with an altered state of consciousness and impaired judgment" (AASM 2005). Bassetti et al. (2000) hypothesized that sleepwalking is a dissociated state, consisting of both mental and motor arousal. Using SPECT, recordings were taken from a 16-year-old man in two conditions: one recording during SWS, the other 24 s after the occurrence of a sleepwalking episode arising from SWS. In both conditions, the patient was injected with ^{99m}Tc-ECD. Compared to undisturbed SWS, there was an increase in rCBF post-sleepwalking, particularly in the posterior cingulate cortex and the anterior cerebellum (Bassetti et al. 2000). Interestingly, these areas showed a decrease in activity in healthy volunteers during SWS compared to wakefulness (Maquet et al. 2000). Furthermore, Bassetti et al. compared their data to those of control subjects and observed that the patient demonstrated a decrease in perfusion in the frontoparietal associative cortices during the sleepwalking episode compared to wakefulness in controls. This hypoperfusion was interpreted as reflecting a lack of self-related awareness and the inability to recall the

events of the sleepwalking episode. In contrast, the hyperperfusion of the posterior cingulate and cerebellum were thought to reflect persistent arousal patterns, which is in line with the hypothesis of a dissociated state. These findings should be interpreted with caution as they were based on a single individual with sleepwalking.

More recent studies investigated brain function of sleepwalkers during wakefulness. Using ^{99m}Tc-ECD SPECT, Dang Vu et al. scanned 10 adult sleepwalkers during wakefulness in the morning as compared to 12 control subjects and found no difference in brain perfusion between groups (Dang-Vu et al. 2014). However, when scanning again a subsample of these individuals (eight sleepwalkers and nine controls) after a night of total sleep deprivation, they observed a hypoperfusion of the inferior temporal cortex compared to controls. While increased sleep propensity (i.e., sleep deprivation) is known to promote sleepwalking episodes in the following sleep period (Zadra et al. 2008), these SPECT findings revealed a pattern of neural dysfunction characterizing wakefulness in sleepwalkers after sleep deprivation (Dang-Vu et al. 2014). A few years later, the same team revealed that after total sleep deprivation, sleepwalkers (ten adults) showed reduced rCBF in left parietal and temporal regions and increased rCBF in right parahippocampal gyrus during resting-state wakefulness compared to ten control subjects (Desjardins et al. 2018). Moreover, during the SWS period following the total sleep deprivation, sleepwalkers displayed reduced perfusion in the left insula, postcentral gyrus, and superior temporal gyrus (Desjardins et al. 2018). Combined with the findings from 2015, these results are in line with the increased vulnerability of sleepwalkers to sleep deprivation.

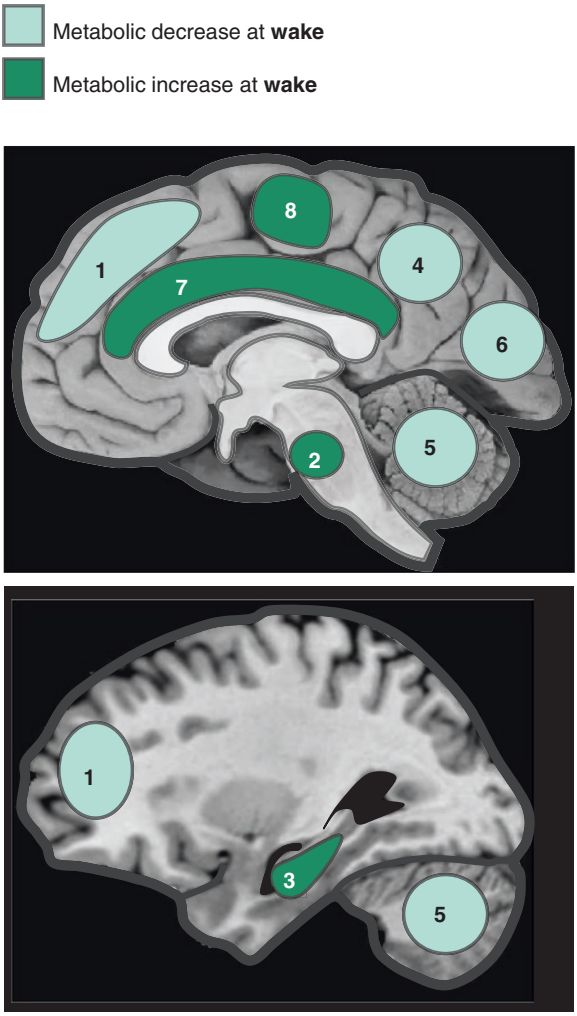
33.4.2 REM Sleep Behavior Disorder

Within REM parasomnias, RBD is accompanied by a loss of skeletal muscle atonia usually present during REM sleep and involves complex motor activity occurring specifically in association with dream mentation. The disorder is characterized by unpleasant dreams and dream enactment, which could be disturbing to the patient or the bed partner (AASM 2005). RBD can exist with or without a medical condition, respectively known as secondary RBD or idiopathic RBD (iRBD). Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) tend to develop in patients with RBD several years later (Postuma et al. 2009) with an estimate of 41% risk 5 years after RBD clinical manifestations (Postuma et al. 2015) and more than 90% after 14 years (Iranzo et al. 2014). SPECT and PET have played a significant role in highlighting the brain regions involved in RBD pathophysiology and clinical evolution. A summary of these findings on idiopathic RBD is provided in Fig. 33.3.

33.4.2.1 Hypo- and Hyperperfusions in RBD

A study performed by Shirakawa et al. (2002) compared 20 male iRBD patients to 7 healthy male subjects using *N*-isopropyl-*p*-^{123}I-iodoamphetamine (^{123}I-IMP) SPECT. Compared to the control group, a statistically significant decrease of rCBF

Idiopathic RBD



Mazza 2006
1. Superior frontal lobe
2. Pons
3. Right hippocampus
4. Parietal lobe

Vendette 2011
1. Superior frontal lobe
2. Pons
3. Hippocampus (bilaterally)
4. Precuneus

Hanyu 2011
4. Precuneus
5. Cerebellum

Dang-Vu 2012
2. Pons
3. Hippocampus (bilaterally)

Ge 2015
6. Occipital lobe
7. Cingulate
8. Supplementary motor area
2. Pons
3. Hippocampus (bilaterally)

Mayer 2015
1. Premotor area
2. Pons
5. Cerebellum

Fig. 33.3 Brain regions showing hyperperfusion or hypoperfusion in rCBF during wake in iRBD patients. Many of these changes in rCBF mirror those observed in several synucleinopathies. Adapted from Dang-Vu et al. (2014)

was found in the right and left upper portion of the frontal lobe and in the pons. The scans were performed at night, although it was not clear which state of vigilance the subjects were experiencing. A few years later, Mazza et al. (2006) conducted a study using ^{99m}Tc-ECD SPECT, which included eight iRBD patients and nine healthy control subjects. In contrast to Shirakawa et al. (2002), significant hyperperfusions were found in the pons, as well as in the putamen and the right hippocampus. Interestingly, increased rCBF is also present in the latter two regions during the

early stages of PD (Imon et al. 1999). In addition, decreased perfusion was found in the frontal lobe, particularly in motor cortices, and in the temporoparietal cortices. A larger study of 20 iRBD patients and 20 control subjects exhibited similar results (Vendette et al. 2011). Once again using ^{99m}Tc-ECD SPECT, hyperperfusion was displayed in the pons, the putamen, and bilaterally the hippocampus and hypoperfusion in frontal and medial parietal areas.

Hanyu et al. (2011) monitored rCBF using ^{123}I-IMP SPECT in 24 patients with iRBD. In contrast with previous studies, they did not find significant differences between patients and controls in the brainstem and frontal areas. Results did however display hypoperfusion in iRBD patients, in the precuneus, cerebellum, and uncus regions, also identified by Vendette et al. (2011).

In order to investigate longitudinal rCBF alterations, Sakurai et al. (2014) performed repeated ^{123}I-IMP SPECT sessions on nine iRBD patients with a mean interval of 22 ± 9 months between the two scans. Patients were taking medication to treat their symptoms during both scans. They found a decreased rCBF in medial parietooccipital lobe and in the right posterior cingulate during the follow-up SPECT session compared to baseline, in line with a progressing neurodegenerative process. However, they did not reveal any changes in neuropsychological tests (e.g., Geriatric Depression Scale-15, Frontal Assessment Battery Test, Wechsler Memory Scale-Revised: Logical Memory I and II) between the two sessions. It is important to note that most patients were taking medication (e.g., clonazepam) at both sessions to decrease RBD symptoms (Sakurai et al. 2014).

Two studies led by Caselli et al. (2006) and Fujishiro et al. (2010) assessed CMRglu with ^{18}F-FDG PET in subjects with dream enactment behavior. These subjects displayed decreased CMRglu in multiple cortical areas, such as occipital, frontal, parietal, temporal, and cingulate. No polysomnographic recording was performed to confirm a diagnosis of RBD; rather, patients were selected based on questionnaires and interviews only, hence diminishing the validity of the study. However, in 2015, Ge and colleagues confirmed the decreased metabolism in the occipital cortex and lingual gyrus using ^{18}F-FDG PET in 21 iRBD patients and 21 healthy controls. They also found increased metabolism in the supplementary motor area, cingulate, pons, and hippocampus/parahippocampus compared to controls, similarly to perfusion SPECT studies. Interestingly, change in metabolism correlated with clinical measures, including a negative correlation between RDB duration and metabolism in the medial frontal gyrus but a positive correlation between RBD duration and metabolism in the anterior vermis (Ge et al. 2015).

SPECT with ^{99m}Tc-ECD was used to predict the onset of PD and DLB in 20 iRBD patients (Dang-Vu et al. 2012). The average follow-up of 3 years revealed that PD or DLB emerged in ten of the patients; interestingly, only these ten patients showed an increase in hippocampal rCBF at baseline. It can thus be proposed that the progression of idiopathic RBD into PD or DLB can be predicted via abnormal perfusion in the hippocampus.

While the studies above described functional neuroimaging acquired in iRBD patients mainly during wakefulness, only two studies reported brain activations associated with RBD behavioral manifestations. The first one was conducted on a

single man, with multiple system atrophy and RBD, and compared to two healthy control subjects (Dauvilliers et al. 2011). After injecting ^{99m}Tc-ECD *during* a RBD episode, compared to wakefulness, the patient showed increased perfusion in the supplementary motor area, suggesting this area's involvement in the onset of dream enactment behaviors. The effect was not present in controls when contrasting REM sleep vs. wakefulness. Another study performed ictal SPECT with ^{99m}Tc-ECD tracer injected after 10 s of a RBD episode in four RBD patients, including one iRDB patient, one RBD patient with PD, and two RBD patients with narcolepsy. They found activations in the bilateral premotor areas, periaqueductal area, pons, and anterior lobe of the cerebellum in all patients (Mayer et al. 2015). No SPECT data has been obtained so far during REM sleep per se (outside motor manifestations) in RBD patients.

33.4.2.2 Dopaminergic Imaging

Due to the relationship between RBD and PD, multiple system atrophy, and other conditions associated with DA dysfunction (Gagnon et al. 2009), there have been numerous SPECT and PET ligand studies in the last decade analyzing the nigrostriatal DA system in RBD patients. It has been suggested that substantia nigra alteration and reduced DAT update in RBD would be predictive markers for conversion to synucleinopathy. After De Marzi and colleagues found that more than 65% of iRBD patients displayed loss of nigral hyperintensity similar to PD patients using 3.0-T susceptibility-weighted (SW) MRI (De Marzi et al. 2016), Bae et al. (2018) compared the loss of nigral hyperintensity with SW MRI and DAT uptake with iodine 123–2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane (^{123}I-FP-CIT) SPECT to determine whether substantia nigra alteration could predict RBD patients at risk for conversion to PD in 18 patients with iRBD, 18 PD patients, and 18 healthy controls. They found that nigral hyperintensity and DAT uptake ratios were lower in 11 iRBD patients compared to controls but still higher than PD patients. Within these 11 iRBD patients with low nigral hyperintensity, 5 developed symptoms of synucleinopathy within 18 months, suggesting that SW imaging might be a useful tool to detect RBD patients with high risk for short-term conversion (Bae et al. 2018).

A group performed two SPECT studies with ^{123}I-IPT demonstrating a decrease in DAT at the presynaptic site of the striatum in iRBD patients compared to age- and sex-matched controls (Eisensehr et al. 2000, 2003a). Additionally, these two studies also included an assessment of postsynaptic D2 receptor binding using ^{123}I-IBZM SPECT and found no significant change in iRBD compared to controls and PD. This suggests that DA dysfunction in the striatum is restricted to the presynaptic level in RBD patients, in line with a loss of DA midbrain neurons, and similarly to findings in PD (Tatsch et al. 1997). Similar results were found when using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) PET in 6 iRBD patients compared to 19 controls (Albin et al. 2000). Similarly, a PET study was performed using (+)-[^{11}C]dihydrotetrabenazine (^{11}C-DTBZ) tracer to measure presynaptic striatal binding and (-)-5-[^{123}I]iodobenzovesamicol ([^{123}I]IBVM) SPECT to assess thalamic cholinergic binding in 13 patients with probable MSA and presence of RBD. Compared to 27

healthy controls, the MSA-RBD patients showed a decrease in thalamic cholinergic binding as well as a decrease in striatal binding, which was negatively correlated with the severity of REM atonia (Gilman et al. 2003). Whether it is the degeneration of nigrostriatal DA neurons that contribute to RBD symptoms in MSA needs to be investigated with a comparison between MSA patients with and without RDB symptoms.

In agreement with the studies conducted by Eisensehr et al. (2000, 2003a, b), the density of striatal DAT was measured, and a decrease in presynaptic binding was found, most prominently in the posterior putamen. This was later confirmed by Li and colleagues who used ^{99}mTc-TRODAT-1 SPECT on 43 patients with iRBD. They found that the 18 patients with decrease DAT uptake in the left striatum and putamen at baseline converted to a full-blown synucleinopathy (i.e., 2 DLB, 3 MSA, 13 PD) after a median of 4.1 years of follow-up (median interval of 10.5 years from the estimated iRBD symptoms onset) (Li et al. 2017). Using ^{18}F-DOPA PET on 20 patients with iRBD and 19 healthy controls, Stokholm and colleagues investigated nigrostriatal dopaminergic function and also revealed reduced uptake bilaterally in the putamen but not in caudate (Stokholm et al. 2017). Moreover, using ^{11}C-(*R*)-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline-carboxamide (^{11}C-PK11195) PET on the same patients, they investigated whether neuroinflammation (i.e., increase in peripheral benzodiazepine receptor translocator protein binding expressed by activated microglia) usually shown in synucleinopathies was also present in RBD. They found increased microglial activation in the left substantia nigra but not in the putamen and caudate. They did not find correlation between dopaminergic deficit and neuroinflammation. Because only a subset of patients actually revealed abnormally high level of microglial activation in the substantial nigra, they proposed that future studies should investigate whether the presence of neuroinflammation in RDB patients might represent a marker of conversion to synucleinopathies (Stokholm et al. 2017). Four studies examined DAT in RBD patients using SPECT with ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane (^{123}I-FP-CIT). Two studies in particular concluded that an insignificant number of RBD patients demonstrated a decrease of striatal DAT (Stiasny-Kolster et al. 2005; Unger et al. 2008).

Another report compared 14 idiopathic RBD patients, 14 early-stage Parkinson's disease, and 12 controls (Kim et al. 2010). Further confirming the studies performed by Eisensehr and colleagues (2000, 2003a), the RBD patients showed lower binding in the striatum compared to control subjects, more specifically in the putamen. This binding was however higher compared to Parkinson's disease patients, suggesting a progressive DA impairment from RBD to Parkinson's disease. In a more recent ^{123}I-FP-CIT SPECT study, 43 idiopathic RBD and 18 controls were examined longitudinally for striatal DAT (Iranzo et al. 2010). It was found that there was reduced binding in 40% of the RBD patients. This study included a follow-up demonstrating that a neurodegenerative disorder developed in eight of the IRBD patients within 2.5 years after the imaging took place. Interestingly, six of these eight patients had reduced DAT at baseline, highlighting the significance of lowered DAT in the prediction of disease evolution.

A case study involving a 73-year-old man used ^{11}C-CFT to assess changes of nigrostriatal presynaptic DA 1 year and 3.5 years after the onset of RBD (Miyamoto et al. 2010). Compared to controls, the first year's results displayed only a minor decrease in the posterior putamen, yet after 3.5 years, there was a more pronounced decrease of 4–6% per year. Similarly, a recent 3-year study used ^{123}I-FP-CIT SPECT on 20 IRBD patients (Iranzo et al. 2011). Complementary to the case report, there was a reduction in binding over time (compared to controls) in all striatal regions with the exception of the right caudate nucleus, further demonstrating a progressive nigrostriatal dopaminergic dysfunction. Alteration in the substantia nigra over time has been reported with diverse neuroimaging techniques including MRI (De Marzi et al. 2016).

Overall, these data suggest that iRBD are in line with the concept of RBD as a "prodromal" phase of synucleinopathies. However, RDB can also occur after PD diagnosis or never at all, which lead to the question whether a distinct RBD phenotype of PD might exist. Arnaldi and colleagues (2015a, b) investigated dopaminergic deafferentation using ^{123}I-FP-CIT-SPECT in 12 patients with iRBD, 16 PD patients without RBD (at baseline and at clinical follow-up), and 24 PD patients with RBD (symptoms at baseline or present during follow-up). They found that PD patients with presence of RBD revealed lower DAT striatal binding and more severe motor impairment than PD patients without RBD. Moreover, by computing caudate specific binding ratio (caudate SBR; i.e., caudate DAT uptake minus background DAT uptake), they observed that PD patients without RBD showed preserved nigro-caudate functioning compared to iRBD patients and PD patients with RBD suggesting that nigro-caudate deafferentation could be the hallmark of RBD. In comparison, nigro-putamen deafferentation (i.e., putamen SBR) observed in PD patients with and without RBD would represent an hallmark of PD severity as it is relatively preserved in iRBD patients but progressively altered in PD along with progressive motor impairment (Arnaldi et al. 2015b). Future studies might take into consideration the presence or absence of RBD in PD patients as it might explain some of the divergent results found in studies comparing iRBD and PD patients.

Because of its relationship with synucleinopathies, iRBD has been extensively studied with a focus on DA dysfunction. However, only one study investigated possible alteration in the serotonergic system in iRBD. Indeed, it has been shown that antidepressants, especially serotonin reuptake inhibitors (SSRI), can lead to loss of atonia during REM (induced-RDB) suggesting possible abnormal serotonergic system integrity. Using ^{123}I-FP-CIT-SPECT in 20 iRBD patients and 23 healthy controls, they assessed DAT uptake in caudate and putamen as well as serotonin transporter (SERT) uptake in the midbrain, pons, and thalamus. As expected, they found lower striatal binding in iRBD compared to controls but found no difference in SERT uptake at the brainstem and thalamic levels (Arnaldi et al. 2015a).

33.4.2.3 Metabolic Brain Networks

Beyond single region alterations, recent studies focused on metabolic brain networks using ECD-SPECT and/or FDG PET imaging. More specifically PD exhibits stereotyped changes in brain structure and function that is associated with a highly

reproducible disease-related metabolic brain network called PD-related covariance pattern (PDRP) and includes increased metabolic activity in the internal globus pallidus, thalamus, pons, and cerebellum as well as reduction in premotor and parietal regions. This increased PDRP expression is associated with progressive motor impairment (Eidelberg 2009). Recent studies found that PDRP expression is increased in some patients with RBD suggesting higher risk for conversion to PD. More precisely, Holtbernd and colleagues used resting-state ^{18}F-FDG PET on a cohort of 10 iRBD patients and 10 healthy controls as well as resting-state ^{99m}Tc-ECD SPECT on a cohort of 17 iRBD patients and 17 healthy controls and performed annual follow-up clinical assessment for 4.6 (±2.5) years after baseline imaging. They found that PDRP expression (i.e., metabolic activities in pons, cerebellum, putamen/globus pallidus, thalamus, sensorimotor, lateral premotor, and parietal association cortex) was increased in iRBD patients compared to controls in both PET and SPECT imaging. Moreover, 8 iRBD patients (out of the 17 with follow-up) were diagnosed with PD or DLB, and 3 developed signs of probable MSA (Holtbernd et al. 2014). In another study also using ^{18}FDG PET, Meles et al. (2017) also found higher PDRP expression in 21 iRBD compared to 19 healthy controls but lower compared to 20 PD patients and 22 patients with DLB. Interestingly, more than half of the RBD subjects revealed PDRP expression in the range of PD patients. In the same study, they also used DAT-SPECT and olfactory testing to offer a more complete assessment of iRBD patients at risk for conversion. Indeed, both loss of DAT binding and hyposmia symptoms have been associated with high risk for developing synucleinopathies (Mahlknecht et al. 2015). PDRP and striatal DAT binding were not significantly correlated in iRBD patients, but they found that PDRP expression was higher in iRBD patients presenting hyposmia ($N = 9$) compared to iRDB without hyposmia (Meles et al. 2017). Whether the presence of high PDRP expression, low striatal DAT binding, and hyposmia might reflect higher risk for phenoconversion needs to be assessed.

Beyond PDRP expression, Wu et al. (2014) showed that RBD patients might also exhibit its own unique metabolic network as well. Indeed, using ^{18}FDG PET on 21 iRBD patients and 21 healthy controls, they found that iRBD-related metabolic network would be characterized by increased metabolic activity in pons, thalamus, medial frontal areas, hippocampus, supramarginal/inferior temporal gyri, and posterior cerebellum with reduced activity in occipital and superior temporal regions. When compared with 21 hemi-PD patients (i.e., early PD with only one clinically symptomatic side) and 16 patients with moderate PD, they found that the iRBD-related metabolic network was also increased in hemi-PD patients compared to controls and slightly lower compared to iRBD (although not significant). Compared to iRBD, moderate PD showed a decreased expression in iRBD-related metabolic network compared to iRBD but higher PDRP expression compared to iRBD and hemi-PD (Wu et al. 2014). Future studies need to assess whether this iRBD-related metabolic network might reflect a prodromal phase of PD and predict those with higher risk of phenoconversion.

33.4.3 Summary

Sleepwalking demonstrates brain patterns reminiscent of both SWS and wakefulness states, therefore appearing as a dissociated state. Moreover, alterations in brain perfusion during wakefulness and SWS after sleep deprivation might reflect the neural correlates underlying the increased propensity of sleepwalking episodes when lacking sleep. Additional studies are needed to further qualify the role of SWS alterations in somnambulism.

In iRBD patients, SPECT and PET have shown a presynaptic dysfunction of DA nigrostriatal pathways, further indicating that iRBD represents the early stages of PD, DLB, and multiple system atrophy. Moreover, the risk of progression from iRBD to other neurodegenerative disorders can be estimated using SPECT. Hypoperfusions found in the pons agree with human studies involving pontine lesions in RBD pathophysiology (Culebras and Moore 1989; Gomez-Choco et al. 2007; Kimura et al. 2000; Limousin et al. 2009; Plazzi and Montagna 2002; Provini et al. 2004; Schenck and Mahowald 2002; Tippmann-Peikert et al. 2006; Xi and Luning 2009; Zambelis et al. 2002). The role of structures such as the hippocampus and cognitive aspects of RBD should be further investigated. Finally, brain activity patterns during behavioral episodes and during sleep should be further examined to shed new light on the pathophysiology of RBD.

33.5 Insomnia

33.5.1 Primary Insomnia

Primary insomnia is defined by as a dissatisfaction with sleep quality and complaints of difficulties falling asleep and/or maintaining sleep and/or waking up early with the incapacity to fall back asleep occurring more than three times a week for over a month. Moreover, often accompanied by a feeling of fatigue and daytime functioning impairments, these difficulties cannot be attributed to any medical or psychiatric cause, drug abuse, or other sleep disorders (e.g., sleep apnea) (Sateia 2014). The diagnosis of primary chronic insomnia is applied when the patient complains of sleep difficulties at least three times a week for more than 3 months (ICSD-3). Sleep loss—especially when it becomes chronic—is impairing, as it can have consequences on physical and mental health (Bonnet and Arand 2007), including increased risk for depression (Tsuno et al. 2005). Insomnia affects about 40% of the population on a temporary basis and more than 10% of the population in a persistent/chronic manner (Chung et al. 2015) and thereby represents a major health issue.

Electroencephalography (EEG) and functional and structural imaging have contributed much to the current scientific knowledge of insomnia. Many studies have been conducted using functional and structural MRI, with various applications

(e.g., voxel-based morphometry (VBM) and proton magnetic resonance spectroscopy (^{1}H-MRS) (Cross and Dang-Vu 2019; Desseilles et al. 2011; O'Byrne et al. 2014)). In this section we will focus on the studies using PET and SPECT in primary insomnia (see Fig. 33.4) and then fatal familial insomnia.

Only a few studies have recorded brain activity during NREM sleep in order to assess the functional neuroanatomy of primary insomnia. In order to measure regional brain metabolism (indexed by CMRglu) during waking and NREM sleep, Nofzinger et al. (2004b) used ^{18}F-FDG PET in 7 patients with primary insomnia

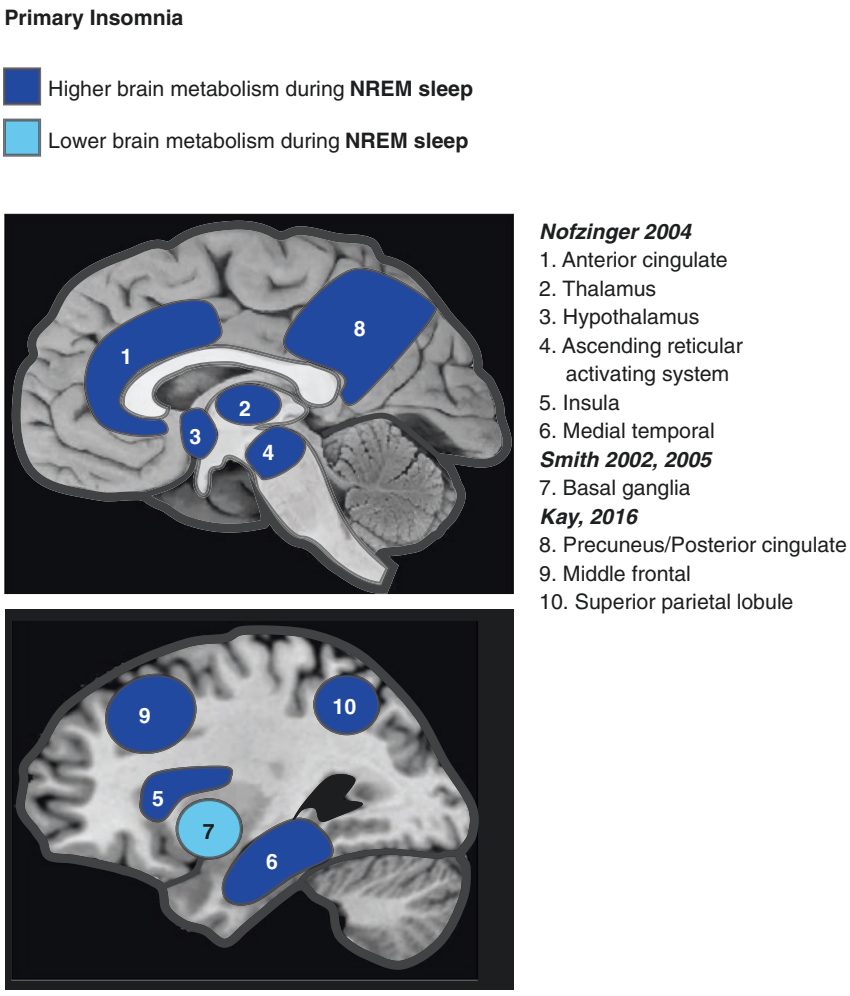


Fig. 33.4 Regional cerebral metabolism reduction and increase during NREM sleep in primary insomnia compared to good sleepers. Kay and colleagues suggested that the smaller decline in glucose metabolism from wake to NREM might represent an impaired disengagement during NREM sleep. Adapted from Dang-Vu et al. (2014)

(i.e., sleep difficulties for more than 1 month) and 20 healthy age-matched and gender-matched subjects. During the transition from waking to NREM sleep, insomnia patients showed (1) a global CMRglu increase as compared to healthy subjects, suggesting that there is an overall cortical hyperarousal in insomnia; (2) less reduction of relative CMRglu in the ascending reticular activating system, hypothalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices; and (3) an increased metabolism in the thalamus, which might reflect persistent sensory processing and information processing as well as subsequent shallower sleep. In contrast, during wakefulness, patients with insomnia showed a decreased metabolism in subcortical (thalamus, hypothalamus, and brainstem reticular formation) as well as in cortical regions (prefrontal cortex bilaterally, left superior temporal, parietal, and occipital cortices).

In 2016, the same team used ^{18}F-FDG PET to scan a larger sample, including 44 patients with primary insomnia and 40 good sleepers, during both morning wakefulness and NREM sleep at night. They did not find any whole-brain glucose metabolism difference between groups, and both groups showed significantly lower whole-brain glucose metabolism during NREM sleep than during wake. However, they found group-by-state interactions in relative regional CMRglu in the precuneus/posterior cingulate cortex, left middle frontal gyrus, left inferior/superior parietal lobules, left lingual/fusiform/occipital gyri, and right lingual gyrus, suggesting that insomniacs have a smaller decline than healthy sleepers during NREM sleep compared to wake or a smaller increase during wake compared to NREM sleep in these clusters. They argue that such smaller decline from wake to NREM might represent an impaired disengagement during NREM and consequently a lack of regionally restorative sleep in these specific regions. Consequently, this could explain the daytime cognitive-affective symptoms of insomnia as these regions are involved in cognitive (i.e., left frontoparietal), self-referential (i.e., precuneus/posterior cingulate), and affective (i.e., left middle frontal, fusiform/lingual gyri) processes (Kay et al. 2016).

If we consider these findings together, they indicate that insomnia might involve elevated regional brain activity during sleep due to smaller differences in brain metabolism between NREM and wake. In both studies, the smaller increase in prefrontal cortex activity during wakefulness compared to controls is consistent with (1) reduced attentional abilities and impaired cognitive flexibility resulting from inefficient sleep and (2) a chronic state of sleep deprivation (Drummond et al. 2001; Durmer and Dinges 2005; Thomas et al. 2000).

In order to estimate rCBF during NREM sleep, another early study by Smith et al. (2002) compared five patients with chronic primary insomnia (in this study, defined by sleep difficulties for more than 6 months) with four normal sleepers using SPECT, employing technetium-^{99m}-hexamethylene-propyleneamine oxime (^{99m}Tc-HMPAO). No significant regional increase has been shown during this period, but a reduced rCBF was observed in frontal medial, occipital, and parietal cortices, as well as in the basal ganglia. This result suggests that primary insomnia is associated with an abnormal pattern of regional brain function during NREM sleep that particularly involves basal ganglia. It is interesting to notice that Nofzinger

et al. (2004b) had also found decreases in activity in these same regions in patients with primary insomnia, but during wakefulness. It is necessary to consider two methodological limitations in Smith's study. Both concern the timing of blood flow measurement: (1) it was only sampled during the first NREM cycle, and (2) it was measured after a longer duration of NREM sleep in insomniac patients than in healthy subjects. The consequence of the first limitation is that the decreased metabolism in insomniac patients might reflect a cortical hypoarousal during the initial phases of NREM sleep following sleep onset. However, it is still possible that the patients were more aroused over later NREM sleep cycles, which would be more consistent with higher beta activity later at night (Perlis et al. 2001). The second limitation leads to a possible underestimation of activity in the patients because blood flow decreases over long NREM periods. Because of such methodological limitations, these preliminary results cannot rule out the hyperarousal hypothesis of idiopathic insomnia. Cognitive behavioral therapy including sleep restriction and stimulus control was applied in the Smith's study, and four of the insomniac patients were rescanned after they had been treated by this therapy (Smith et al. 2005). After treatment, there was a reduction of at least 43% in the sleep latency, and a global 24% increase in CBF, with a significant increase in the basal ganglia. The authors proposed that such an increase in brain activity might reflect the normalization of sleep homeostatic processes. These promising results will certainly inspire further investigations on the effects of psychotherapy on brain functioning in insomnia.

33.5.2 Fatal Familial Insomnia

Fatal familial insomnia (FFI) is a hereditary or sporadic disease caused by a prion protein gene mutation. This illness is invariably lethal (Lugaresi et al. 1986). It is characterized by insomnia, autonomic hyperactivity, and motor abnormalities (Lugaresi et al. 1986; Montagna et al. 2003). The disrupted sleep pattern is characterized by a loss of sleep spindles and SWS and enacted dreams during REM sleep (Montagna et al. 2003).

In a study by Perani et al. (1993), four awake patients were investigated using PET and ^{18}F-FDG. The analysis revealed a prominent hypometabolism in the anterior part of the thalamus. There were two types of clinical presentation. Two patients exhibited symptoms restricted to insomnia and dysautonomia. Thalamic hypometabolism was found isolated in one subject, accompanied by a frontal, anterior cingulate and temporal polar hypometabolism in the other. In the two patients with a more complex clinical presentation, hypometabolism was more widespread and involved many cortical areas, the basal ganglia and the cerebellum. This widespread pattern was already present at an early stage of the disease and was found significantly aggravated as the disease progressed in one patient, examined twice several months apart. However, it is not known whether this widespread hypometabolism is indicative of the more advanced stages of the disease or whether it indicates two forms of this disorder, one thalamic and the other disseminated.

In another study by Cortelli et al. (1997), seven patients with FFI were investigated using ^{18}F-FDG and PET to examine regional cerebral glucose utilization. All FFI patients presented a severely reduced glucose utilization of the thalamus and a mild hypometabolism of the cingulate cortex. In six of these subjects, brain hypometabolism also affected the basal and lateral frontal cortex, the caudate nucleus, and the middle and inferior temporal cortex. Further comparison between homozygous ($n = 4$) or heterozygous ($n = 3$) patients at codon 129 showed that the hypometabolism was more widespread in the heterozygous group, which had a significantly longer symptom duration at the time of ^{18}F-FDG PET study. Comparison between neuropathological and ^{18}F-FDG PET findings in six patients showed that areas with neuronal loss were also hypometabolic. However, cerebral hypometabolism was more widespread than expected from histopathological changes and significantly correlated with the presence of protease-resistant prion protein. Neuroimaging results indicate that hypometabolism of the thalamus and cingulate cortex is a common feature of FFI, while the involvement of other brain regions depends on the duration of symptoms and some unknown factors specific to each patient (Cortelli et al. 1997). Even in a case of atypical FFI, thalamic hypometabolism was confirmed as an early marker, while cortical changes vary with clinical presentation and stage (Bar et al. 2002). More recently, serotonin transporters of two FFI patients were examined with ^{123}I-β-CIT SPECT as compared to age-expected control values (Kloppel et al. 2002). This study showed a reduced availability of serotonin transporters of 57% and 73%, respectively, in a diencephalic region of the two FFI patients. Although this finding suggests an involvement of serotonin neurotransmission, it is not clear whether it is causal in FFI pathogenesis (Kloppel et al. 2002).

In another study by Cortelli et al. (2006), 9 asymptomatic carriers of the D178N mutation, 10 noncarriers belonging to the same family, and 19 age-matched controls were studied over several years in order to examine how and when the degenerative process begins. The CMRglu was measured with ^{18}F-FDG PET in parallel with detailed clinical, neuropsychological examinations and polysomnography with EEG spectral analyses. All cases at the beginning of the study had a normal CMRglu as well as normal clinical and electrophysiological examinations. Concerning the mutation carriers, four of them developed typical FFI over the course of the study. On the other hand, their CMRglu and their clinical and electrophysiological examinations remained normal 63, 56, 32, and 21 months before disease onset. The carrier whose tests were normal 32 months before disease onset was reexamined 13 months before onset. A selective hypometabolism in the thalamus was shown at that time, while an abnormality in thalamic sleep spindle formation was detected by spectral EEG analysis. Following clinical disease onset, CMRglu was reduced in the thalamus in all three patients examined. The data of the study suggest that the neurodegenerative process associated with FFI begins in the thalamus between 13 and 21 months before clinical presentation of the disease.

33.5.3 Neuroimaging of Sleep in Depression

A pioneering study by Ho et al. (1996) examined the first NREM period in 10 unmedicated patients with unipolar depression and in 12 healthy controls. The depressed patients showed higher CMRglu during NREM sleep in the pons, posterior cingulate, amygdala, hippocampus, and occipital and temporal cortices. There was a significant reduction of relative CMRglu in medial orbital frontal and anterior cingulate cortices, caudate nucleus, and medial thalamus. These early findings support the hypothesis that hyperarousal in depression affects a network of limbic and posterior cortical regions, but also that the decreased medial frontal and striatal metabolism may be a hallmark of depression (Drevets et al. 1997).

In a first study by Nofzinger et al. (1999), six unipolar depressed subjects and eight healthy subjects underwent separate ^{18}F-FDG PET scans during waking and during their first REM period of sleep. Changes in CMRglu from waking to REM sleep were assessed in each group as well as interactions in patterns of change between groups. Compared to the control subjects, depressed patients in this study did not show increases in CMRglu in anterior paralimbic structures in REM sleep compared to waking. Depressed subjects did, however, show greater increases from waking to REM sleep in CMRglu in the tectal area and a series of left hemispheric areas including the sensorimotor cortex, inferior temporal cortex, uncal gyrus-amygdala, and subicular complex than did the control subjects. These observations suggest that changes in limbic and paralimbic function from waking to REM sleep differed significantly between normal and depressed patients.

The second Nofzinger et al. investigation (2000) focused on the association between EEG measures and ^{18}F-FDG PET measures in depressed patients. The study was undertaken in 9 healthy controls and 12 depressed subjects. The main findings were that beta power negatively correlated with subjective sleep quality for both healthy and depressed subjects. Beta frequency oscillations in EEG are high-frequency, low-amplitude neural oscillations associated with behavioral arousal and attentional processes, observed mostly in waking and REM sleep (Nofzinger et al. 2000). In both depressed and healthy subjects, beta EEG was positively associated with CMRglu in the ventromedial prefrontal and lateral inferior occipital cortices. There was a trend, in the depressed group, for beta power to correlate positively with relative whole-brain metabolism during NREM sleep (first NREM sleep cycle). For the depressed group only, beta EEG was also positively correlated with CMRglu in the left dorsolateral prefrontal cortex and amygdala/uncal gyrus regions.

More recent studies have confirmed that depressed patients have relatively persistent "elevated" activity measured by CMRglu across many brain regions during sleep compared to pre-sleep wakefulness (REM, 24 depressed patients compared to 14 controls; NREM, 12 depressed patients compared to 13 controls). As shown in Fig. 33.5, regions more activated during REM sleep included frontal, parietal, premotor, and sensorimotor cortices, as well as the insula, the ventral pallidum, and the midbrain reticular formation (Nofzinger et al. 2004a). Regions more activated during NREM sleep included the temporal and occipital cortices, as well as the insula, posterior cingulate, cerebellum, and thalamus (Germain et al. 2004). However,

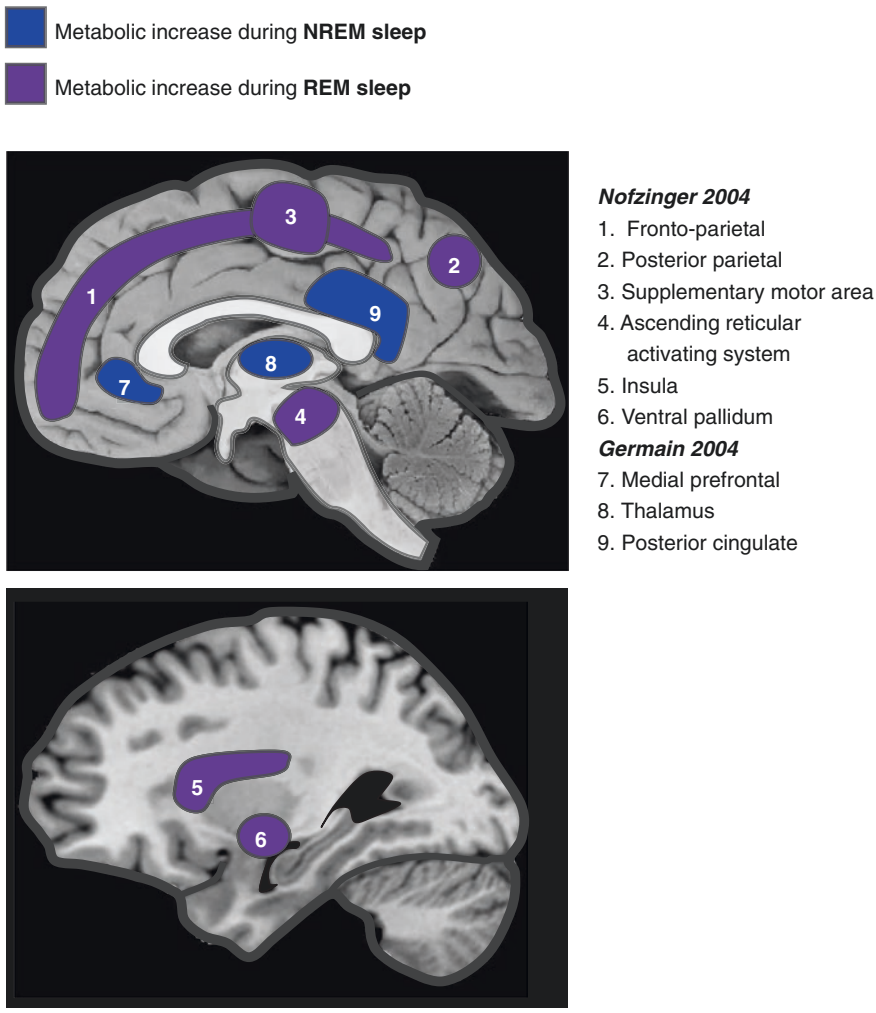


Fig. 33.5 Metabolic changes during REM and NREM sleep in depression. During NREM (Germain et al. 2004) and REM (Nofzinger et al. 2004a), depressed patients showed "elevated" activity measured by CMRglu across several cortical and subcortical regions in sleep compared to pre-sleep wakefulness. Adapted from Dang-Vu et al. (2014)

increased metabolism was also found in prefrontal cortex, unlike Ho et al. (1996). These results are again consistent with a general hyperactivation of arousal systems in depression that may underlie both sleep disturbances such as insomnia and non-restorative sleep complaints in depressed patients.

Increased rapid eye movement density (number of REMs per minute of REM sleep) was found to correlate with depression severity and clinical outcomes (Buysse

et al. 1999).In humans, REM bursts are classically thought to reflect ponto-geniculo-occipital (PGO) waves, possibly associated with orienting responses and arousal processes during sleep (Peigneux et al. 2001; Wehrle et al. 2005). An ^{18}F-FDG PET study assessed cerebral glucose consumption in a group of 13 medication-free depressed patients during REM sleep (Germain et al. 2004). The average REM count (an automated analog of REM density) was found to positively correlate with metabolism in a network of regions involved in emotional regulation and emotion-induced arousal (medial and ventrolateral prefrontal cortex) as well as in regions linking emotion and attention systems (striate cortex, precuneus, and posterior parietal cortex). Whether increased activity in these regions drives hyperarousal during REM sleep remains unclear. These results might not be specific to depression, because no control data were provided in that study and because the observed activation pattern overlapped with results of healthy controls from other studies (Braun et al. 1998; Peigneux et al. 2001).

33.5.4 Summary

Because currently available data are limited and not perfectly consistent, any conclusion about the cerebral correlates of insomnia during NREM sleep must remain tentative. While there is some evidence for decreased activity in cortical areas during early NREM sleep as well as during wakefulness, several subcortical regions involved in sleep/wake regulation, including limbic and paralimbic regions, were found to be more active during the transition from waking to sleep states. Current data generally support the hyperarousal theory of insomnia, with increased neuronal activity during NREM sleep as a possible key factor contributing to sleep misperception and disturbances occurring in insomnia.

Depression is often associated with insomnia, as well as with hyperarousal characterized by persistent "elevated" activity across many brain regions during NREM sleep, but also during REM sleep. Strong evidence for hyperarousal in both primary insomnia and depression, together with persistent alterations in sleep architecture in remitted depression, corroborate common neurophysiological mechanisms underlying sleep and mood regulation.

33.6 General Conclusions

Functional neuroimaging is a compelling tool that provides unprecedented possibilities to explore brain function during normal and pathological sleep. PET and SPECT studies have provided many insights into the neurobiological bases of sleep pathologies, which are strongly linked to the regulation of mood, emotion, and decision-making. Narcoleptic patients seem to have decreased hypothalamic and thalamic activity, in line with a hypocretin dysfunction and altered vigilance, with increased activity in the amygdala and cingulate cortex, which may be related to

abnormal emotional processing. Nuclear imaging in narcolepsy type 2 (i.e., without cataplexy) remains to be investigated. Recent findings in idiopathic hypersomnia suggested preserved hypocretinergic system but lower activity in medial prefrontal cortex and posterior cingulate cortices, suggesting possible intrusion of NREM-like features during wakefulness in idiopathic hypersomnia. For RLS and PLM, hypoactivity in pre- and postsynaptic DA transmission in the striatum and SN may underlie the compulsive limb movements. RBD patients show changes in activity in the pons, hippocampus, frontal lobes, and striatum, suggesting that an altered nigrostriatal dopaminergic activity in RBD might predict conversion to Parkinson's disease and Lewy body dementia. Hyperactivity throughout many brain regions during NREM sleep in insomnia is also observed in depression, suggesting common pathophysiological mechanisms underlying both disorders.

Even with these insights, functional neuroimaging in sleep medicine is still in its infancy. Methodological issues such as small sample sizes and omitted control groups limit the reliability of some studies, including case studies. Furthermore, technical issues involved in imaging patients during sleep, particularly in movement disorders, have impeded the progress of new studies. As the field matures, advanced multimodal neuroimaging and improved experimental designs will allow observations to be made at additional timepoints of these disorders, with larger sample sizes and control groups, and will therefore further characterize the pathophysiological mechanisms of sleep disorders and the functional consequences of long-term sleep disruption. PET and SPECT will finally be essential to examine and monitor the neural effects of current and future pharmacological compounds targeting sleep disorders.

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