PET and SPECT in Sleep Disorders

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R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_34, © Springer-Verlag Berlin Heidelberg 2014

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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 displayed decreased hypothalamic and thalamic perfusion during resting wakefulness, which may be related to hypocretinergic deficiency and altered vigilance. 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 Parkinson's disease. 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.

34.1 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; Maquet et al. 1990; Steriade and McCarley 1990). 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. Deactivations were present in the dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex (Braun et al. 1997; Maquet 2000; Maquet et al. 1996, 2005; Nofzinger et al. 1997). 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 specificities of PET and SPECT measures in imaging 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. 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 (Dang-Vu et al. 2007, 2009; Desseilles et al. 2008).

34.2 Narcolepsy

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness. Other frequent symptoms include transient loss of muscle tone triggered by emotions (cataplexy), sleep paralysis, and hypnagogic hallucinations. Individuals diagnosed with this disorder tend to have unstable sleep at night, with frequent 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 narcoleptics is the human leukocyte antigen (HLA) subtype DQB1*0602. More specific is the central deficiency in the hypothalamic peptide hypocretin-1, reflected by low levels in the cerebrospinal fluid, particularly in narcoleptic patients who present episodes of cataplexy. Hypocretinergic dysfunction is thought to underlie the unstable sleep–wake transitions and impaired vigilance in narcolepsy–cataplexy (Dauvilliers et al. 2007).

Neuroimaging techniques have been applied to narcolepsy 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 functional studies point to disturbed hypothalamic and limbic activity, consistent with reduced vigilance, hypocretinergic dysfunction, and abnormalities in emotional processing. A summary of these findings is provided in Table 34.1 and Fig. 34.1.

34.2.1 Acetylcholine, Serotonin, and Dopamine Functions in Narcolepsy

Sudo et al. (1998) focused on ACh neurotransmission in narcolepsy. 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 narcoleptics 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 narcolepsy–cataplexy. They used PET with 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p*-^{18}F-fluorobenzamidoethylpiperazine (^{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 using ^{123}I-(*N*)-(3-iodopropene-2-yl)-2b-carbomethoxy-3b-(4-chlorophenyl) tropane (^{123}I-IPT) SPECT (Eisensehr et al. 2003b) 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 narcoleptics and controls. When looking at postsynaptic D2 receptor binding, a study found a difference between narcoleptic 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 increased D2 binding in the striatum in seven narcoleptics. 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

Table 34.1 PET and SPECT studies in narcolepsy, 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

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. (2003b)	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. (2003b)	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
McFarlane 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
Yeon Joo et al. (2005)	SPECT ^{99m}Tc-ECD	rCBF	25/25	0/25	Reduced cerebral perfusion in hypothalami
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 brain stem. Decreased perfusion in prefrontal cortex and occipital lobe

(continued)

Table 34.1 (continued)

Study	Imaging technique employed	Target	Number of patients/ controls	Patients receiving treatment/ total number of patients	Results
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

dopamine and narcolepsy 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.

34.2.2 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 in particular assessed the CMRglu of 24 narcoleptic patients and 24 normal individuals using PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). They found that narcoleptics had reduced CMRglu in the bilateral posterior hypothalami and mediodorsal thalamic nuclei (Joo et al. 2004). However, this study did not include EEG measurements, for vigilance monitoring. Another study used SPECT with ^{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 (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 mid-cingulate 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.

34.2.3 Neural Correlates of Cataplexy

Given the inherent difficulty in "catching" a narcoleptic patient in the scanner during a cataplectic episode, few studies have examined brain activity during cataplexy

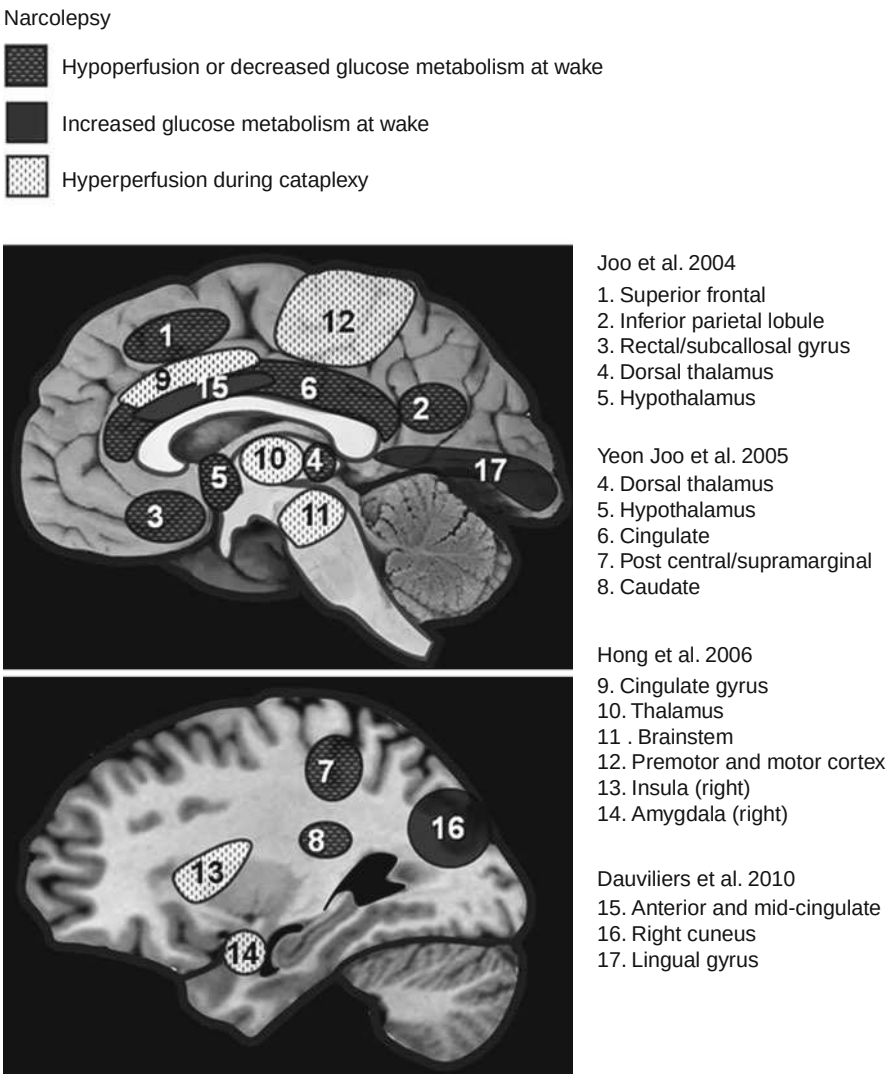

Fig. 34.1 Brain regions showing differences in CMRglu or rCBF during wakefulness in narcolepsy, as well as hyperperfusion (rCBF) during cataplectic attack (Adapted from Desseilles et al. (2008))

(loss of muscle tone). A study was conducted using technetium-99m ethylcysteinate dimer (^{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 narcoleptic patients using 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.

34.2.4 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 narcoleptic patients.

34.2.4.1 Methylphenidate

Methylphenidate, an amphetamine derivative, is commonly used for treating narcolepsy. One SPECT study used ^{133}Xe inhalation to examine rCBF in narcoleptic individuals 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.

34.2.4.2 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 narcoleptic patients were in the awake state, both before and after a 4-week treatment with either modafinil or 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 narcoleptic patients (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). Seven

narcoleptics patients 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.

34.2.5 Summary

Generally, SPECT and PET studies did not demonstrate a consistent difference in ACh, DA, or 5-HT neurotransmission in narcolepsy. 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 post-treatment 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 narcoleptic patients.

34.3 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.

34.3.1 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 ^{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). The discrepancy in these findings may be attributable to particular pharmacokinetic properties of radioligands used in PET and SPECT. Earley and colleagues (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 and colleagues (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 and colleagues (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.

34.3.2 Periodic Limb Movements

Dopaminergic transmission has been studied in relation to PLM. At the presynaptic level, Happe and colleagues (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).

34.3.3 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.

34.4 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.

34.4.1 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) and culminate in walking around with an altered state of consciousness and impaired judgment" (AASM 2005). To date, there is only a single case studying sleepwalking with neuroimaging. 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 was thought to reflect persistent arousal patterns, which is in line with the hypothesis of a dissociated state. Further studies should confirm these findings using a larger sample size.

34.4.2 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. Parkinson's disease, dementia with Lewy bodies (DLB), and multiple system atrophy tend to develop in patients with RBD several years later (Postuma et al. 2009). SPECT and PET have played a significant role in highlighting the brain regions involved in RBD pathophysiology and clinical evolution (Fig. 34.2).

A study performed by Shirakawa et al. (2002) compared 20 male idiopathic RBD 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 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 they were experiencing.

Mazza et al. (2006) conducted a study using ^{99m}Tc-ECD SPECT, which included eight idiopathic RBD 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 Parkinson's disease (Imon et al. 1999). In addition, decreased perfusion was found in the frontal lobe, particularly in the motor cortices and in the temporo-parietal cortices. A larger study of 20 idiopathic RBD patients and 20 control subjects exhibited similar results (Vendette et al. 2011). Once again using ^{99m}Tc-ECD SPECT, hyperperfusion was displayed in pons, putamen, and bilaterally in 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 RBD patients, in the precuneus, cerebellum, and uncus, regions also identified by Vendette and colleagues (2011).

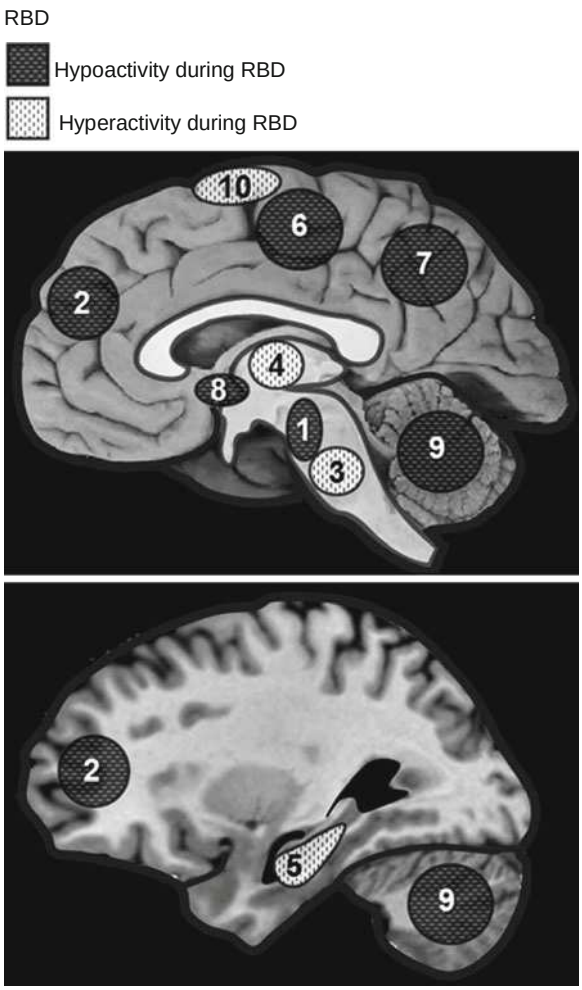

Fig. 34.2 Brain regions showing hyperperfusion or hypoperfusion in rCBF during wakefulness (except for Dauvilliers et al. (2011), which was conducted during a RBD episode in REM sleep) in RBD patients. Many of these changes in rCBF mirror those observed in the early stages of Parkinson's disease (Adapted from Desseilles et al. (2008))

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.

SPECT with ^{99m}Tc-ECD was recently used to predict the onset of PD and DLB in 20 idiopathic RBD 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, 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 RBD patients mainly during wakefulness, only one study reported brain activations associated with RBD behavioral manifestations. This study was conducted on a single patient, 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 versus wakefulness. No SPECT data was obtained during REM sleep outside the behavioral episode in RBD patients.

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. A group performed two SPECT studies with ^{123}I-IPT demonstrating a decrease in DAT at the presynaptic site of the striatum in idiopathic RBD 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 RBD 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).

The same conclusion was reached in a PET study using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) in a study comparing 6 idiopathic RBD patients to 19 controls (Albin et al. 2000). In agreement with the studies conducted by Eisensehr and colleagues (2000, 2003a), the density of striatal DA was measured, and a decrease in presynaptic binding was found, most prominently in the posterior putamen.

Similarly, another PET study was performed using ^{11}C-DTBZ to measure presynaptic striatal binding. The 13 patients who had RBD and probable multiple system atrophy showed a decrease in binding, which was negatively correlated with the severity of REM atonia (Gilman et al. 2003). These results suggest that a presynaptic DA deficit might contribute to the frequent occurrence of RBD in patients with multiple system atrophy.

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, 6 of these 8 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 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.

34.4.3 Summary

Several SPECT and PET neuroimaging studies are available for RBD. However, to date, only one study has been devoted to sleepwalking. Sleepwalking demonstrates brain patterns reminiscent of both SWS and wakefulness states, therefore appearing as a dissociated state. Additional studies are needed to further qualify the role of SWS alterations in somnambulism.

In RBD patients, SPECT and PET have shown that there exists a presynaptic dysfunction of DA nigrostriatal pathways, further indicating that RBD represents the early stages of PD, DLB, and multiple system atrophy. Moreover, the risk of progression from RBD 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 examined to shed further light on the pathophysiology of RBD.

34.5 Insomnia

34.5.1 Idiopathic Insomnia

Insomnia is a common disorder in our society. Ten to twenty percent of the general population reports insomnia complaints and related problems of daytime functioning (Ohayon and Hong 2002). The AASM (2005) defines insomnia as a common symptom or syndrome including difficulty in initiating or maintaining sleep, or

"unrefreshing" sleep. This causes significant problems in several areas, including mood, motivation, attention, and vigilance. According to the ICSD (ICSD-2), idiopathic insomnia is a persistent failure to obtain adequate sleep that is probably due to an abnormal neurological control of the sleep–wake system (AASM 2005). Depression is often associated with insomnia (Tsuno et al. 2005).

Electroencephalography (EEG) and functional and structural imaging have contributed much to the current scientific knowledge of insomnia. In this section we will focus on the studies using PET and SPECT in idiopathic and fatal familial insomnia. Some other studies have been conducted using fMRI (e.g., (Altena et al. 2008)) and structural MRI, with various applications (e.g., voxel-based morphometry (VBM) and proton magnetic resonance spectroscopy (^{1}H-MRS)) (Desseilles et al. 2008).

Only a few studies have recorded brain activity during NREM sleep in order to assess the functional neuroanatomy of idiopathic insomnia disorder. 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 idiopathic insomnia 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, as illustrated in Fig. 34.3; 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, insomnia patients 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). If we consider these findings together, they indicate that insomnia might involve particularly elevated regional brain activity during the transition to sleep, with a localized decline in brain metabolism during wakefulness. The observed reduction in prefrontal cortex activity during wakefulness 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 insomniacs with four normal sleepers using SPECT, employing technetium-99 m-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 (Fig. 34.3). This result suggests that idiopathic 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 insomnia patients, but during wakefulness. It is necessary to consider methodological specificities in Smith's study. For instance, blood flow measurement was only sampled during the first NREM cycle. Therefore, the decreased metabolism in insomnia patients might reflect a cortical hypoarousal during the initial phases of NREM sleep following sleep onset.

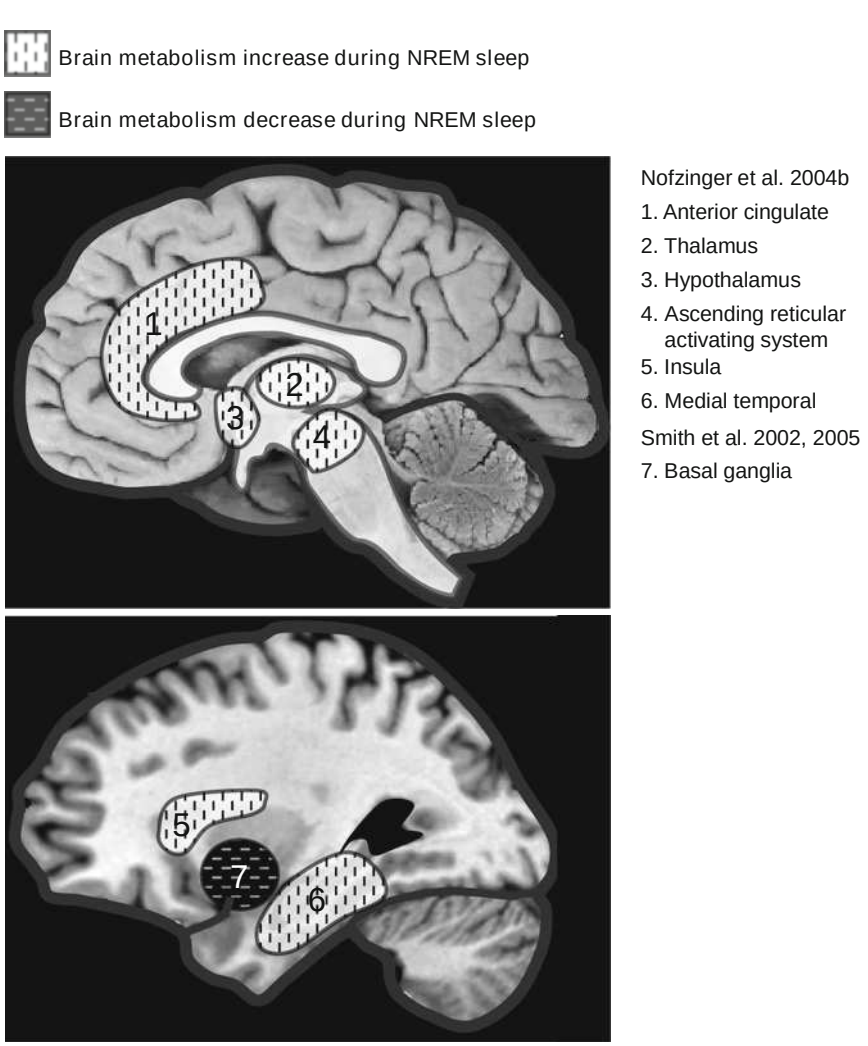

Fig. 34.3 Regional cerebral metabolism during NREM sleep in idiopathic insomnia. Nofzinger et al. (2004b) found increased regional metabolism (^{18}F-FDG PET) during NREM sleep in patients with idiopathic insomnia. Smith et al. found reduced regional cerebral blood flow (SPECT) in the basal ganglia in insomniacs (Smith et al. 2002, 2005) (Adapted from Desseilles et al. (2008))

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). Thus, these results cannot rule out the hyperarousal hypothesis of idiopathic insomnia. Cognitive behavioral therapy including sleep restriction and stimulus control was applied in Smith's study, and four of the insomnia 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.

34.5.2 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 ($n=4$) and 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), nine asymptomatic carriers of the D178N mutation, ten 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 cerebral metabolic rate of glucose (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 3 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.

34.5.3 Neuroimaging of Sleep in Depression

A pioneering study by Ho et al. (1996) examined the first NREM period in ten 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 nine 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. 34.4, 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, 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 as well as nonrestorative 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).

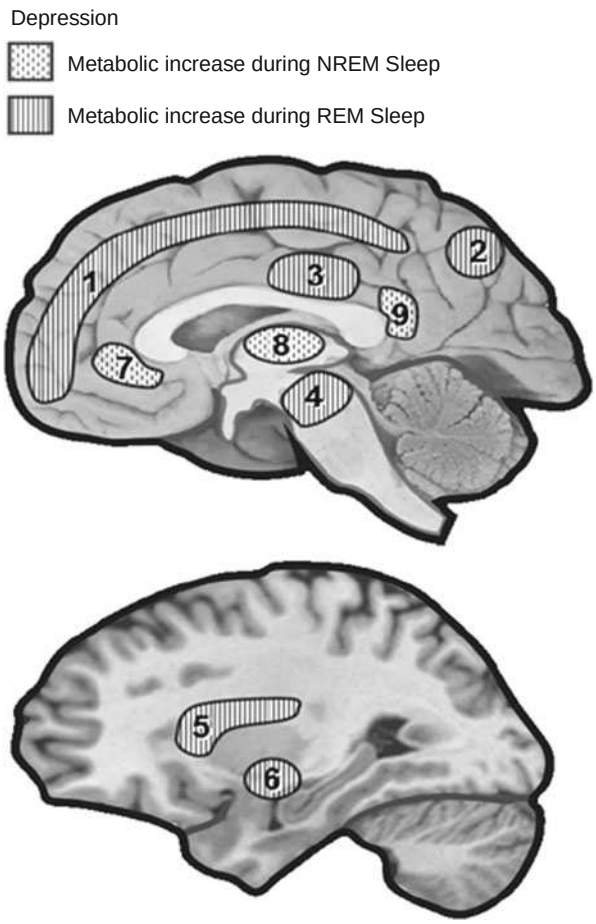

Fig. 34.4 Metabolic changes during REM and NREM sleep in depression. During NREM (Germain et al. 2004) and REM (Nofzinger et al. 2004a), depressed patients showed "elevated" activity measured by CMRglu across several cortical and subcortical regions in sleep compared to pre-sleep wakefulness. *1* frontoparietal, *2* posterior parietal, *3* supplementary motor area, *4* ascending reticular activating system, *5* insula, *6* ventral pallidum, *7* medial prefrontal, *8* thalamus, *9* posterior cingulate (Adapted from Desseilles et al. (2008))

34.5.4 Summary

Because currently available data are limited and not perfectly consistent, any conclusion about the cerebral correlates of insomnia during NREM sleep has to 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 idiopathic insomnia and depression, together with persistent alterations in

sleep architecture in remitted depression, corroborates common neurophysiological mechanisms underlying sleep and mood regulation.

34.6 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. 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 blood flow in the pons, frontal lobes, striatum, and hippocampus, linking this disorder to later onset of Parkinson's disease. 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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