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Sleep and Movement Disorders

Neuroimaging Aspects

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BRAIN IMAGING techniques, such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), have characterized the specific distribution of cerebral activity for each stage of sleep in healthy subjects (for review, see Maquet,[1] Dang-Vu et al.[2]). Functional neuroimaging studies have demonstrated regional increases and decreases of brain activity in areas responsible for the generation of rapid eye movement (REM) sleep and some important characteristics of dreams.[3] During non-REM sleep, as compared to wakefulness, they have evidenced mostly decreases of brain responses, in various associative cortical areas and subcortical structures.[1] Beyond sleep stages, recent fMRI studies have also described the neural responses associated with brain oscillations of sleep.[4] In particular, they have shown increased brain responses associated with spindles and slow waves of non-REM sleep, demonstrating that non-REM sleep is not merely a passive state of brain deactivation.[5,6] Altogether these data have refined our understanding of the mechanisms and functions of normal human sleep.

An increasing number of neuroimaging studies dedicated to the disorders of sleep have been published in the last decade (for review, see Dang-Vu et al.,[2] Desseilles et al.[7]), bringing an important contribution to the pathophysiology of sleep disorders. For instance, in the case of narcolepsy-cataplexy, brain imaging studies have shown structural and functional abnormalities in the hypothalamus and multiple associative cortical areas, in agreement with a loss of hypocretinergic neurons in this disease.[8]

In this chapter, we will focus on neuroimaging studies of sleep-related movement disorders. We will consider specific sleep disorders such as restless legs syndrome (RLS), often associated with periodic limb movements during sleep (PLMS), and parasomnias taking place either during non-REM sleep (such as sleepwalking) or REM sleep (REM sleep behavior disorder [RBD]). Several neurological disorders associated with specific sleep disturbances, such fatal familial

insomnia (FFI), and specific epileptic syndromes occurring during sleep, such as nocturnal frontal lobe epilepsy (NFLE), benign epilepsy with centrotemporal lobe spikes (BECTS), Landau-Kleffner syndrome (LKS), and the syndrome of continuous spike-and-wave discharges during slow-wave sleep (CSWS), will also be discussed.

We will review the brain imaging studies published to date in each of these disorders. Various modalities have been used and will be considered successively. These include neuroanatomical studies using magnetic resonance imaging (MRI) to analyze changes in gray matter with voxel-based morphometry (VBM), white matter changes with diffusion tensor imaging (DTI), or neuronal integrity with proton magnetic resonance spectroscopy (^{1}H-MRS). Functional studies were carried out with single photon emission computed tomography (SPECT), PET, and fMRI to assess brain responses throughout the sleep-wake cycle (mostly during wakefulness) or in association with symptomatic events. Finally, SPECT and PET were also coupled with specific ligands to measure local neurotransmitter function, such as for dopamine (DA).

It should be noted that acquiring brain imaging data in patients with movement disorders constitutes in many instances a technical challenge. The presence of movements during acquisition produces artifacts both on structural and functional sequences. Techniques such as SPECT, however, allow scan acquisition to be performed well after the radio-labeled compound has been injected during the episode of interest, therefore minimizing the interference of movements on the imaging procedure.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS

Restless Legs Syndrome

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a nearly irresistible urge to move the lower limbs (less frequently the upper limbs), usually associated with a discomfort sensation deep inside the limbs, which is exacerbated by rest or inactivity, especially when lying or sitting at evening or night.[9,10] Around 94% of patients report sleep-onset insomnia or nocturnal awakenings due to RLS-related symptoms, which is corroborated by patterns of disrupted sleep at polysomnography.[11] RLS can present as an isolated phenomenon (i.e., *idiopathic* forms) or being *secondary* to other medical conditions.[9,10] Among these latter forms, the one associated with iron deficiency anemia is by far the most common. Multiple interacting mechanisms seem to underlie this disease, including various cortical and subcortical brain structures, the spinal cord, the peripheral nervous system, and multiple biochemical pathways and neurotransmitter systems. Nevertheless, the exact pathophysiological "puzzle" of RLS has not been solved so far.[12] Important clues on RLS pathophysiology have arisen from clinical experience and point to a role for iron metabolism and dopaminergic system.[13,14] Neuroimaging studies of RLS have investigated the changes in brain anatomy and function associated with this condition.

STRUCTURAL NEUROIMAGING

Structural brain imaging studies of RLS are summarized in Table 19.1.

VBM and DTI Studies. Structural abnormalities in RLS were studied with MRI, using a VBM approach. A first study comparing 51 RLS patients to 51 controls evidenced a gray matter increase in the dorsal thalamus bilaterally, in a region compatible with the pulvinar nuclei.[15] Another VBM study, conducted on a larger sample of 63 patients (and 40 controls), found decreases of gray matter in primary sensorimotor cortices.[16] Interestingly, gray matter values in these cortical areas were also negatively correlated with RLS severity and disease duration.[16] The same group also investigated differences in white matter in 45 RLS patients (compared to 30 controls), using MRI with DTI sequences.[17] In line with their previous study, they found white matter alterations in the vicinity of sensorimotor cortices and in thalamic structures. These findings of sensorimotor thalamocortical pathways alterations in RLS seem to be in line with the patients' description of their symptoms. Whether these changes reflect neural mechanisms underlying the disease or secondary changes induced by chronic afferent input still needs to be elucidated. Additionally, patients in these three studies were medicated, mostly with dopaminergic agents, which might have affected the results. In favor of this last interpretation, three other VBM studies conducted on unmedicated patients showed no significant change between RLS and controls,[18–20] with the exception of a slight gray matter increase in the hippocampus and orbitofrontal gyrus.[18] The

Table 19.1 Structural Neuroimaging of Restless Legs Syndrome

STUDY	IMAGING	NO. PAT. // CTRL.	MEDICATION*	RESULTS
Etgen et al.[15]	MRI / VBM	51 // 51	Yes	GM increase in dorsal thalamus
Unrath et al. [16]	MRI / VBM	63 // 40	Yes	GM decreases in primary sensorimotor cortices
Unrath et al. [17]	MRI / DTI	45 // 30	Yes	WM changes near sensorimotor and thalamic areas
Hornyak et al. [18]	MRI / VBM	14 // 14	No	Slight GM increase in hippocampus and orbitofrontal gyrus
Celle et al. [19]	MRI / VBM	17 // 54	No	No difference
Comley et al.[20]	MRI / VBM	16 // 16	No	No difference
Allen et al. [24]	MRI / R2	5 // 5	Yes	Decrease of iron concentration in SN
Earley et al. [25]	MRI / R2	41 // 39	No	Decrease of iron concentration in SN, for early-onset RLS
Godau et al. [26]	MRI / R2 & TCS	6 // 19	No	Decrease of iron concentration in SN, thalamus, and caudate
Schmidauer et al. [29]	TCS	20 // 20	Yes	Decrease of iron concentration in SN
Godau et al. [28]	TCS	49 // 49	Yes	Decrease of iron concentration in SN

*Medication at the time of imaging (mostly dopaminergic agents).

DTI, diffusion tensor imaging; GM, gray matter; MRI, magnetic resonance imaging; RLS, restless legs syndrome; SN, substantia nigra; TCS, transcranial ultrasound; VBM, voxel-based morphometry; WM, white matter.

number of patients was, however, much lower in these these studies (ranging from 15 to 17), which could have contributed to a lack of significant difference between RLS and controls.

Iron Studies. Iron metabolism has been suggested to play a crucial role in RLS pathophysiology. Indeed, RLS association with iron deficiency is well known. Moreover, iron is

closely associated to the DA system since it is an important cofactor for tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis.[21] Furthermore, a decrease of ferritin level in cerebrospinal fluid has been found in RLS,[22] while neuropathologic studies have shown a reduction of H-ferritin (ferritin heavy chain) and iron staining in the substantia nigra (SN) of these patients.[23] MRI studies have brought additional evidence for a central iron deficiency in RLS. In a study of five idiopathic RLS patients compared to five controls, Allen and colleagues have shown a decrease of iron concentration in SN, as reflected by R2' measurements on MRI sequences.[24] Iron decrease correlated with RLS severity from clinical scales. Another study from the same group confirmed this finding on a higher sample of patients ($n = 41$) and additionally showed that the decreased iron concentration in SN was restricted to early-onset RLS patients (<45 years; $n = 22$).[25] An MRI study from a different group using similar measurements in a small sample of six RLS patients showed decreased iron concentrations in other brain areas such as thalamus and caudate, suggesting that central iron deficiency might be multiregional rather than limited to SN only.[26] Iron brain concentration can also be assessed by transcranial ultrasound (TCS), since echogenicity of SN is associated with local iron content.[27] Three studies using this technique have consistently shown a hypoechogenicity of SN in RLS patients, further supporting the evidence for a reduction of iron concentration in this area.[26,28,29]

FUNCTIONAL NEUROIMAGING

fMRI Studies. Few studies have attempted to describe the neural mechanisms underlying RLS using functional brain imaging with fMRI. In an early fMRI study, seven idiopathic RLS patients were scanned during periods of sensory leg discomfort. During these symptomatic periods, there was a bilateral activation of the cerebellum and a contralateral activation of the thalamus.[30] Recently a preliminary study used fMRI with simultaneous leg electromyography (EMG) to assess the brain responses associated with tonic EMG at rest in seven RLS patients.[31] Indeed, tonic EMG was found inversely correlated with subjective sensory leg discomfort, thereby providing an objective reflection of RLS symptoms. This study showed that tonic EMG was positively correlated with fMRI response in sensorimotor cortical areas, cingulate gyrus, precuneus and occipital cortex, and negatively correlated in the cerebellum.[31] Altogether these preliminary results suggest an involvement of thalamocortical sensorimotor pathways, in agreement with several VBM studies cited earlier, as well as additional structures (including cerebellum) in the pathophysiology of RLS.

SPECT and PET Ligand Studies. Most functional neuroimaging studies of RLS have used SPECT or PET in association with various radio-labeled compounds to assess neurotransmission abnormalities (Table 19.2). Two systems were of particular interest: DA and opiate systems. Indeed, dopaminergic agents and opioids constitute the main therapeutic options in RLS patients.[32] SPECT and PET studies have explored both presynaptic DA transporter (DAT) and postsynaptic D2-receptor binding, mainly in the striatum. Striatal DAT reflects the density of DA neurons in SN. SPECT studies using ^{123}I-2betacarbomethoxy-3beta-(4-iodophenyl) tropane(^{123}I-β-CIT)[33,34]or^{123}I-N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane (^{123}I-IPT) [35,36] failed to demonstrate any difference in DAT between RLS and controls. In contrast with SPECT data, PET studies using ^{18}F-dopa [37,38] or ^{11}C-methylphenidate [39] found decreased presynaptic DA function in the striatum of RLS compared to controls. This discrepancy might be due to distinct pharmacokinetic properties of the different SPECT and PET compounds. In the recent PET study with ^{11}C-methylphenidate from Earley and coworkers, RLS patients were scanned either in the morning ($n = 20$) or in the evening ($n = 16$), which allowed the researchers to assess the diurnal differences in DAT.[39] No significant difference was observed between patients scanned in the morning and those scanned in the evening, which suggests that DAT is not modulated by time of day. Furthermore, there was no significant correlation between DAT binding and RLS symptom severity. Results for postsynaptic D2-receptor binding were also quite divergent. ^{123}I-iodobenzamide (^{123}I-IBZM) SPECT found no change[35,40,41] or a mild decrease[33] of striatal D2-receptor binding in RLS patients compared to controls. PET using ^{11}C-raclopride showed either a decreased[37] or an increased [42] D2-receptor binding in the striatum. Differences between these two studies might be related to the inclusion of RLS patients

Table 19.2 SPECT- and PET-Ligand Studies in Restless Legs Syndrome

STUDY	IMAGING	TARGET	NO. PAT. // CTRL.	MEDICATION*	RESULTS
Michaud et al.[33]	SPECT 123I-β-CIT & 123I-IBZM	DAT & D2	10 // 10	No	No change in DAT, decrease in D2
Mrowka et al.[34]	SPECT 123I-β-CIT	DAT	6 // 7	Yes	No change
Eisensehr et al.[35]	SPECT 123I-IPT & 123I-IBZM	DAT & D2	14 // 10	No	No change
Linke et al.[36]	SPECT 123I-IPT	DAT	14 // 23	No	No change
Turjanski et al.[37]	PET 18F-dopa and 11C-raclopride	DAT & D2	13 // 14	Yes	Decrease in DAT and D2
Ruottinen et al.[38]	PET 18F-dopa	DAT	9 // 27	No	Decrease in DAT
Earley et al.[39]	PET 11C-methylphenidate	DAT	36 // 34	No	Decrease in DAT
Tribl et al.[40]	SPECT 123I-IBZM	D2	14 // 9	No	No change
Tribl et al.[41]	SPECT 123I-IBZM	D2	14 // 10	No	No change
Cervenka et al.[42]	PET 11C-raclopride & 11C-FLB457	D2	16 // 16	No	Increase in D2
von Spiczak et al.[44]	PET 11C-diprenorphine	Opioid receptor	15 // 12	No	No change

*Medication at the time of imaging (mostly dopaminergic agents).

D2, dopaminergic D2-receptor binding; DAT, dopamine transporter binding; PET, positron emission tomography; SPECT, single photon emission computed tomography.

who had been exposed to DA drugs in the first study, while patients in the second study were naïve to DA drugs. Indeed, chronic D2 receptor stimulation by drug treatment has been shown to induce receptor downregulation, thereby resulting in lower radioligand binding.[43] In the study of Cervenka and colleagues, RLS patients (n = 16) were also scanned with PET using ^{11}C-FLB457, which allowed the researchers to measure D2-receptor binding in extrastriatal structures.[42] Increased binding potential in RLS patients was found not only in the striatum but also in the thalamus, insula, and anterior cingulate cortex. Since increased receptor levels can be caused by receptor upregulation in response to depletion of endogenous DA, this study is consistent with a hypoactive DA neurotransmission in RLS. The areas showing changes in D2 receptor binding are part of the medial nociceptive system, which regulates the affective component of pain. Therefore, these results are in agreement with the view of RLS as a disorder of somatosensory processing. Finally, since scans were performed both in the morning and evening, the authors were able to evaluate the diurnal changes in D2 receptor binding. Interestingly, they found no significant change between evening and morning scans.[42] In addition, there was no significant correlation between D2 receptor binding

and RLS symptom ratings. Therefore, both presynaptic [39] and postsynaptic [42] studies suggest that diurnal variations in RLS symptoms (being prominent in the evening and night) as well as symptom severity cannot be explained by parallel changes in DA neurotransmission. As regards the opiate system, only one study has compared RLS and controls using PET with ^{11}C-diprenorphine (a nonselective opioid receptor radioligand).[44] Although some correlations were found between ligand binding and RLS severity or pain scores in multiple brain areas, no significant difference in opioid receptor binding was found between patients and controls. This result is in agreement with the available data suggesting that the efficacy of opioids in the treatment of RLS may not be related to specific deficiencies of the endogenous opioid system but rather mediated by DA.[45]

Periodic Limb Movements

Periodic limb movements (PLMs) are stereotyped repetitive movements occurring at rest, which typically involve extension of the big toe, often in combination with partial flexion of the ankle, knee, and sometimes hip. They can occur during sleep (PLMS) or during wakefulness (PLMW) and both PLMS and PLMW can coexist in the same subject.[10] RLS frequently associates with the presence of PLMS or PLMW, but PLMS and PLMW are themselves nonspecific, occurring in other sleep disorders (narcolepsy, sleep apnea, etc.) and in healthy individuals.[46] Because of the frequent association of RLS and PLMS/PLMW, most neuroimaging studies have considered these conditions together. Only a few have attempted to consider PLMs in a more specific way.

In their fMRI study cited earlier, Bucher and colleagues not only scanned RLS patients during periods of sensory leg discomfort but also scanned them in a combined leg discomfort and PLMW condition.[30] While leg discomfort alone induced brain responses in the thalamus and cerebellum, combined sensory symptoms and PLMW were associated with an additional activation in the red nuclei and brainstem (12 patients). When these patients were instructed to voluntarily imitate PLMW, there was no activation of the brainstem but instead an activation of the motor cortex and globus pallidus. These results suggested a subcortical origin for PLM, involving red nucleus and other brainstem structures.

Dopaminergic neurotransmission has also been investigated in association with PLM. One study has assessed striatal presynaptic DA transmission in 11 patients with Parkinson's disease (PD) using SPECT with ^{123}I-β-CIT.[47] As expected, they found a robust reduction in striatal binding values in PD compared to healthy controls. Importantly, these patients were also recorded with polysomnography, which allowed measuring the number of PLMs during their sleep. A negative correlation was found between the number of PLMs and striatal binding values, suggesting that a presynaptic DA deficiency might be involved in the generation of PLMs in PD. At the postsynaptic level, Staedt and colleagues conducted a few studies assessing D2-receptor binding in the striatum of patients with PLMS, using SPECT using ^{123}I-IBZM.[48–50] They found a lower D2-receptor occupancy in PLMS patients.[48,49] This pattern can be corrected by DA replacement therapy, which also leads to an improvement in sleep quality.[50]

Summary

Neuroimaging findings in RLS and PLMs can be summarized as follows:

1. RLS is associated with alterations in *thalamus*, *sensorimotor* cortical areas, and *cerebellum*, as evidenced by functional and some structural brain imaging studies.
2. Functional studies suggest a *subcortical* origin for PLMs, encompassing structures located in the brainstem.
3. MRI and ultrasound studies are consistent with a central *iron* deficiency in RLS patients, located in SN and possibly other subcortical structures.
4. A hypoactivity of DA neurotransmission can be found in the striatum at both pre- and postsynaptic levels in patients with RLS and PLMs.

If RLS and PLMs still appear as complex conditions involving various brain areas and mechanisms, neuroimaging studies seem to demonstrate a deficiency in the DA system, in association with a depletion of iron concentration in SN, which ultimately affects brain structures responsible for sensorimotor control. Future studies are needed to confirm these findings and extend them to unexplored aspects of RLS and PLM pathophysiology, such as brain activity patterns during sleep itself (e.g., for PLMS).

PARASOMNIAS

Parasomnias are defined as undesirable physical events and experiences occurring during entry into sleep, within sleep, or during arousals from sleep. They are classified according to the sleep stage from which they arise and therefore divided into two main categories: REM and non-REM sleep-related parasomnias.[10]

Non-REM Parasomnias

Non-REM parasomnias are also referred to as *arousal parasomnias*, to indicate that they come out at state transitions from non-REM sleep—and especially from slow-wave sleep (SWS)—to wakefulness. They include different subtypes: sleepwalking, confusional arousals, and sleep terrors. Common features are automatic behaviors and the lack of full awareness or memory of the behavioral events themselves.[10] Their pathogenesis is hypothesized to rely on a state dissociation, in which non-REM sleep and wakefulness overlap or occur simultaneously[51]: cortical locomotor centers likely exhibit an activity that is dissociated from the neural state of non-REM sleep.[52]

The only neuroimaging study to date in non-REM parasomnias is a single-case ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) SPECT study of a 16-year-old patient with frequent sleepwalking episodes.[53] In this patient, SPECT was acquired in two conditions, each during a separate nighttime recording: during undisturbed SWS and 24 seconds after the onset of a sleepwalking episode arising from SWS. Compared to quiet SWS, sleepwalking was associated with an increased perfusion in the posterior cingulate cortex and in the cerebellum (vermis). Data from awake normal volunteers were also used as a control condition, and a decrease of perfusion was observed in frontoparietal associative cortices during sleepwalking as compared to normal wakefulness. Posterior cingulate cortex, cerebellum, and frontoparietal associative cortices are usually found deactivated during SWS compared to wakefulness in normal volunteers.[1] The brain perfusion patterns found during sleepwalking are therefore in agreement with the hypothesis of a dissociated state, in which certain areas display activities typical of SWS (frontoparietal cortices), while other structures (cerebellum, posterior cingulate) maintain activities similar to wakefulness. In addition, the deactivation of frontoparietal associative areas might also explain the lack of insight and the amnesia typical of sleepwalking episodes.[53] This finding needs to be confirmed on larger samples. It should also be noted that, given the brief duration of sleepwalking episodes, it is difficult to precisely isolate the brain activity patterns of the episode from those of the wakefulness period that follows (in the present study, the injection was done 24 seconds after the onset of the episode, and the electroencephalogram [EEG] at that time showed fast activities resembling wakefulness). Finally, there was no comparison with the patient's own wakefulness and with SWS in normal subjects; inclusion of these conditions is needed to confirm the specificity of the results to the sleepwalking state.

REM Sleep Behavior Disorder

Among REM parasomnias, REM sleep behavior disorder (RBD) is characterized by excessive sustained or phasic muscle activity during REM sleep (REM sleep without atonia), typically associated with unpleasant dreams and dream enactment behaviors.[10] RBD can present as an isolated phenomenon (*idiopathic* or *cryptogenic RBD*) or in association with neurological or general medical conditions (*secondary RBD*). The secondary forms usually occur within the context of some neurodegenerative diseases or narcolepsy,[54] or they can also represent an "incidental" phenomenon within the context of various brain lesions (vascular, demyelinating, tumor, inflammatory, postsurgical, toxic, etc.).[55] Neuroimaging studies, and anatomical MRI in particular, play a pivotal role in the diagnosis of these forms of RBD. Growing evidence in the literature indicates that idiopathic RBD actually represents an early stage of a neurodegenerative process involving the central nervous system.[56–58] The long-term risk for patients with RBD to develop a neurodegenerative disease (especially synucleinopathies: PD, dementia with Lewy bodies, progressive supranuclear palsy, and multiple-system atrophy) has been estimated at around 17.7% at 5 years and 52.4% at 12 years.[59] RBD physiopathology has been explored in relationship with various models of REM sleep regulation in animals. In one of these models, REM sleep regulatory circuits hinge on the so-called *REM-on* and *REM-off* areas, which mainly contain GABA-ergic neurons located in the pontine tegmentum.[60,61] Among REM-on areas, the sublaterodorsal nucleus (SLD) sends projections to interneurons in the brainstem

and spinal cord, which finally exert an inhibitory action on motoneurons, leading to muscle tone suppression during REM sleep. In RBD, lesions to the SLD would be responsible for a disinhibition of motoneurons, resulting in excessive muscle activity during REM sleep.[60,61] This model is corroborated by several human case reports and case series describing RBD occurrence following focal lesions at brainstem level, independently of their origin: ischemic,[62–64] hemorrhagic,[65] neoplastic,[58,66,] demyelinating,[67–69] and inflammatory.[70] In all these observations, lesions involved the pons, usually (when specified) in the medial and tegmental region.

STRUCTURAL NEUROIMAGING

Structural brain imaging studies of RBD are summarized in Table 19.3.

VBM and DTI Studies. Besides these case reports of standard anatomical neuroimaging procedures cited earlier, it was not until very recently that quantification of morphological changes was assessed in RBD patients, for both gray (VBM) and white (DTI) matter. In a first report, Ellmore and colleagues studied five patients with RBD (and without Parkinson disease), five patients with PD at an early stage (and with subclinical or clinical RBD), and seven healthy controls.[71] All subjects underwent MRI, and their data were processed for VBM. The main outcome measures were volumes of caudate and putamen nuclei. There was no significant difference for caudate volume across groups. RBD patients had reduced putaminal volume compared to controls but also, surprisingly, compared to patients with early PD. While these results might be related to changes in DA neurotransmission in RBD and PD (see later), this study is limited by the small sample size. Microstructural changes in the white matter were assessed in an MRI study with DTI scans in 12 patients with idiopathic RBD compared to 12 healthy control subjects.[72] Changes were located in multiple brain areas such as the internal capsule, the left superior temporal lobe, the right occipital lobe, and the fornix. Alterations were also found in the pons, in agreement with animal and human data suggesting a role for pontine lesions in RBD pathophysiology. Finally, changes were observed in the olfactory region and in the SN, in line with the concept of RBD as an early stage of neurodegenerative diseases, especially for PD. Very recently, Scherfler and collaborators conducted a large multimodal MRI study combining both DTI and VBM in 26 patients with idiopathic RBD compared to 14 healthy controls.[73] DTI identified significant changes in the tegmentum of the midbrain and rostral pons, in line with the results of the previous study. VBM detected gray matter increases in the hippocampus bilaterally in RBD patients compared to controls. While the significance of this last finding remains unclear, it is interesting to note that increased hippocampal perfusion has been observed with SPECT in RBD [74] and PD patients[75] (see later).

Spectroscopy. A single case study of a 69-year-old idiopathic RBD patient scanned with ^{1}H-MRS found increased choline/creatine ratio in the brainstem,[76] when compared to values from a previously published group of healthy young subjects.[77]

The specificity of this finding to RBD is quite uncertain, since it could be confounded by other factors such as age (reference values were taken from subjects aged 21–32 years). Indeed, this result was not confirmed by two subsequent larger ^{1}H-MRS studies. Iranzo and colleagues found no differences of metabolic ratios in the midbrain and pontine tegmentum between 15 idiopathic RBD patients and 15 age- and sex-matched healthy controls.[78] A more recent study compared 12 PD patients with RBD to 12 PD patients without RBD and assessed ^{1}H-MRS metabolic ratios in the pons.[79] No significant difference was found between groups. In summary, in contrast to other structural (see earlier) or functional methods (see later), ^{1}H-MRS does not detect consistent alterations in pontine structures of RBD patients.

Transcranial Ultrasound. Increased echogenicity of SN has been associated with PD, and it is thought to reflect the stage of degeneration of this structure.[80] Given that RBD often precedes the onset of a synucleinopathy, several studies have used TCS to assess echogenicity of SN in RBD patients, in order to evaluate whether SN hyperechogenicity (defined as a size of echogenic SN above 0.20 cm^2) could also be consistently found in RBD as it is in PD. A preliminary report investigated five patients with idiopathic RBD and found hyperechogenic SN in two of them.[81] No control subject was recruited. In a subsequent study, Iwanami and colleagues recruited 34 idiopathic RBD patients, 17 PD patients with a history of RBD and 21 control

Table 19.3 Structural Neuroimaging of REM Sleep Behavior Disorder

STUDY	IMAGING	N PAT. // CTRL.	MEDICATION*	RESULTS
Ellmore et al. (2010)[71]	MRI / VBM	5 // 7	No	GM decrease in putamen
Unger et al. (2010)[72]	MRI / DTI	12 // 12	No	WM changes in pons, midbrain, olfactory region, internal capsule, temporo-occipital, fornix
Scherfler et al. (2011)[73]	MRI / VBM & DTI	26 // 14	No	WM changes in pons, midbrain; GM increase in hippocampus
Miyamoto et al. (2000)[76]	MRI / 1H-MRS	1 // 0**	No	Cho/Cr increase in brainstem
Iranzo et al. (2002)[78]	MRI / 1H-MRS	15 // 15	No	No difference in brainstem
Hanoglu et al. (2006)[79]	MRI / 1H-MRS	12 // 12***	Yes****	No difference in brainstem
Unger et al. (2008)[81]	TCS	5 // 0	No	SN hyperechogenicity in 2 pat.
Iwanami et al. (2010)[82]	TCS	34 // 21	No	SN hyperechogenicity in 42% of pat. (9.5% of ctrl.)
Stockner et al. (2009)[83]	TCS	55 // 165	No	SN hyperechogenicity in 37% of pat. (11% of ctrl.)
Iranzo et al. (2010)[84]	TCS	39 // 149	No	SN hyperechogenicity in 36% of pat. (11% of ctrl.)

MRI = magnetic resonance imaging; VBM = voxel-based morphometry; DTI = diffusion tensor imaging; ^{1}H-MRS = proton magnetic resonance spectroscopy; Cho/Cr = choline / creatine ratio; TCS = transcranial ultrasound; GM = grey matter; WM = white matter; SN = substantia nigra.

*Medication at the time of imaging (sleep-modifying or dopaminergic medication).

**Values were compared to a database of controls from another study (Ref. 77).

***In this particular study, patients and controls had Parkinson's disease (with and without REM sleep behavior disorder, respectively).

****Participants were treated with levodopa, but levodopa dosage was matched between groups.

subjects.[82] While 9.5% of the control group showed SN hyperchogenicity, this pattern was found in 42.1% of the idiopathic RBD group, and at an even higher proportion of 52.6% of the PD group. This finding suggested a continuum of SN degenerative changes from RBD to PD.

Another group conducted a study on a larger sample of 55 idiopathic RBD patients and 165 controls and confirmed the higher proportion of SN hyperechogenicity in RBD (37.3%) compared to controls (10.7%).[83] The same group conducted a follow-up study on idiopathic RBD

patients and found that 30% of these patients developed a neurodegenerative disorder (PD, dementia with Lewy bodies or multiple-system atrophy) within 2.5 years.[84] Among those who developed a neurodegenerative disease, 62.5% had SN hyperechogenicity at baseline. This result suggests that TCS could be useful to identify RBD patients at increased risk for the development of full-blown neurodegenerative disorders (see later).

FUNCTIONAL NEUROIMAGING

Regional Brain Activity Patterns. Distribution of brain perfusion in RBD patients was assessed in several studies using SPECT. A first study compared 20 male idiopathic RBD patients to seven healthy elderly men with N-isopropyl-p-^{123}I-iodoamphetamine (^{123}I-IMP) SPECT.[85] Decreased perfusion was found in the superior frontal gyrus and the pons of RBD patients. SPECT scans were performed at night in both groups, but it is not clear in which state of vigilance the subjects were during scan acquisition. Hypoperfusion in the frontal lobe was confirmed in a ^{99m}Tc-ECD SPECT study, along with additional hypoperfusion in temporo-parietal cortices.[74] In this study, which included eight idiopathic RBD patients and nine control subjects scanned during wakefulness, the pons did not display decreased but increased perfusion in RBD patients, a pattern that was also found in the putamen and the right hippocampus. Since hyperperfusion of putamen and right hippocampus is likewise found in the early stages of PD,[75] this pattern is in agreement with the hypothesis of RBD as an early stage of a neurodegenerative disorder. The same group then conducted a larger and independent study on 20 idiopathic RBD patients and 20 controls during wakefulness using the same ^{99m}Tc-ECD SPECT technique.[86] They found that RBD patients displayed decreased perfusion in frontal and medial parietal (precuneus) areas, and increased perfusion in the pons, putamen, and hippocampus bilaterally, which is mostly consistent with their previous results. Interestingly, a recent follow-up study investigated the clinical evolution of these patients over an average period of 3 years, and examined the differences in brain perfusion at baseline (with ^{99m}Tc-ECD SPECT) between those who would later convert to PD or dementia with Lewy bodies and those who would remain clinically stable.[87] Out of 20 RBD patients, 10 converted and displayed increased perfusion in the hippocampus at baseline compared to the 10 remaining patients who did not convert (Fig. 19.1), but also compared to healthy controls matched for age and sex. Furthermore, this study also found an association in RBD patients between hippocampal hyperperfusion and worse clinical scores for motor function and color vision, both associated with neurodegenerative evolution.[87–89] Altogether, these results demonstrate that increased perfusion in the hippocampus constitutes a consistent biomarker for clinical evolution towards neurodegenerative diseases in RBD patients. Another group used ^{123}I-IMP SPECT to study brain perfusion in 24 idiopathic RBD patients and 18 controls.[90] Unlike previous reports, this study did not find any significant difference between groups in the brainstem and frontal areas. However, hypoperfusions were found for the RBD group in the precuneus, cerebellum, and uncus. Discrepancies with previous studies might be related to differences in the acquisition technique (^{123}I-IMP), study population (mostly male patients), or vigilance state/time at which the study was performed (not specified). Two studies assessed brain glucose metabolism with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET in subjects with dream-enactment behavior suggestive of RBD.[91,92] In contrast with the SPECT studies presented earlier, no polysomnographic recording was conducted to confirm a diagnosis of RBD and subjects were selected following questionnaires and interview only, which limits the interpretation of the findings. Decreases of brain glucose metabolism were found in subjects with dream-enactment behavior in multiple cortical areas (occipital, frontal, parietal, temporal, cingulate), and results were discussed in comparison with similar patterns found in patients with neurodegenerative diseases such as dementia with Lewy bodies. Finally, a recent ^{99m}Tc-ECD SPECT study reported the brain perfusion patterns associated with an episode of RBD in a single patient with multiple-system atrophy.[93] Perfusion in the supplementary motor area was increased during the episode as compared to wakefulness. This pattern was not found when comparing REM sleep and wakefulness in two healthy controls. It was concluded that the supplementary motor area might play a role in the generation of dream-enactment behavior in RBD. However, there was no SPECT acquisition during the patient's REM sleep per se (outside the episode) in this study. Future studies including REM

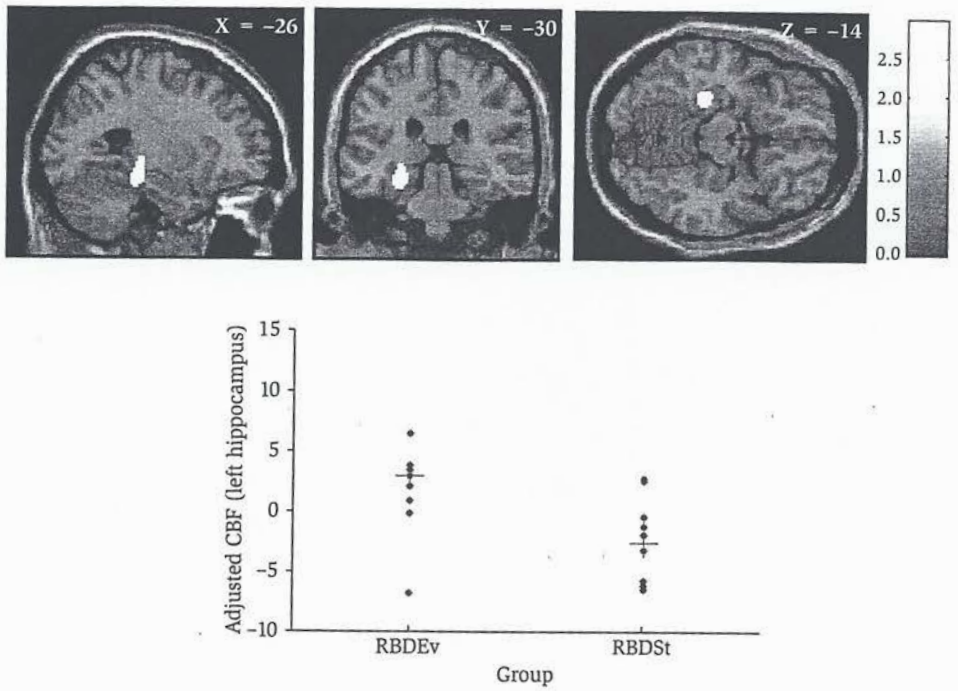

FIGURE 19.1 Hippocampal perfusion predicts clinical evolution in REM sleep behavior disorder (RBD). (Upper panels) Brain perfusion increases at baseline in RBD patients who would convert to neurodegenerative disease (RBDEv), compared to those who would not (RBDSt), were located in the hippocampus. The panels show the peak hyperperfusion, centered on the left hippocampus, and represented on sagittal, coronal and transverse sections (from left to right panels) ($P^{corr} < 0.05$). The level of section is indicated on the top of each panel (x, y, and z coordinates, in mm). The color scale indicates the range of t values for this contrast.
(Lower panel) Plot of the adjusted regional cerebral blood flow values (arbitrary units) in the left hippocampus (x=−30mm, y=−30mm, z=−14mm), showing the distinct distribution in RBDEv and RBDSt patients. Each circle represents one subject. Horizontal bars represent mean values.
This figure shows results from a ^{99m}Tc-ECD SPECT study. (Reproduced from Dang-Vu et al.,[87] with permission.) (*See* color insert.)

sleep assessments and more patients are needed to confirm the specificity of this finding.

SPECT and PET Ligand Studies. Given the frequent association between RBD and conditions associated with a DA dysfunction (such as PD, dementia with Lewy bodies, multiple-system atrophy), several neuroimaging studies have targeted the nigrostriatal DA system in RBD patients (Table 19.4). At the presynaptic level, two SPECT studies with ^{123}I-IPT conducted by the same group demonstrated a decrease of DAT in the striatum of idiopathic RBD patients compared to controls.[94,95] In a first study, DAT in 5 RBD patients was found lower than in 7 controls, but higher than in 14 early-stage PD.[94] In a subsequent report, 8 RBD patients were compared to 8 subjects with "subclinical" RBD (i.e., with loss of muscular atonia during REM sleep in polysomnography, but no behavioral episodes), 11 controls, and 8 early-stage PD.[95] There was a decrease of DAT from controls to subclinical RBD, from subclinical RBD to manifest RBD, and then from RBD to PD. Altogether these results suggest a continuum of striatal presynaptic DA dysfunction in patients with subclinical RBD, clinical RBD, and PD. This finding was confirmed by a PET study using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) to probe the density of striatal DA terminals in 6 idiopathic RBD patients compared to 19 controls.[96] Decreases in striatal binding were found in the striatum, especially in the posterior putamen, in agreement with a presynaptic

Table 19.4 SPECT- and PET-Ligand Studies in REM Sleep Behavior Disorder

STUDY	IMAGING	TARGET	NO. PAT. // CTRL.	MEDICATION*	RESULTS
Eisensehr et al. [92]	SPECT 123I-IPT & 123I-IBZM	DAT & D2	5 // 7	No	Decrease in DAT, no change in D2
Eisensehr et al. [93]	SPECT 123I-IPT & 123I-IBZM	DAT & D2	8 // 11	No	Decrease in DAT, no change in D2
Albin et al. [94]	PET 11C-DTBZ	DAT	6 // 19	Yes	Decrease in DAT
Gilman et al. [95]	PET 11C-DTBZ	DAT	13** // 15	No	Decrease in DAT, neg. correl. with REM atonia loss
Stiasny-Kolster et al. [96]	SPECT 123I-FP-CIT	DAT	11 // 10	Yes	Decrease in DAT in 2 patients
Unger et al. [81]	SPECT 123I-FP-CIT	DAT	5 // 0	No	Decrease in DAT in 2 patients
Kim et al. [97]	SPECT 123I-FP-CIT	DAT	14 // 12	No	Decrease in DAT
Iranzo et al. [84]	SPECT 123I-FP-CIT	DAT	43 // 18	No	Decrease in DAT in 40% of patients
Iranzo et al (link to iranzo 2011)	SPECT 123I-FP-CIT	DAT	20 // 20	No	Decrease in DAT over time
Miyamoto et al. [98]	PET 11C-CFT	DAT	1 // 6	No	Decrease in DAT

* Medication at the time of imaging (sleep-modifying or dopaminergic medication).

** In this particular study, patients had multiple-system atrophy and a history of RBD.

D2, dopaminergic D2-receptor binding; DAT, dopamine transporter binding; PET, positron emission tomography; SPECT, single photon emission computed tomography.

DA impairment in RBD. Interestingly, another PET study using ^{11}C-DTBZ was conducted in 13 patients with probable multiple-system atrophy compared to 15 control subjects.[97] Not only was striatal binding decreased in the patients' group, but binding was also negatively correlated with the severity of REM atonia loss. This finding suggests that presynaptic DA deficit might contribute to the frequent occurrence of RBD in patients with multiple-system atrophy. Four studies assessed presynaptic DAT in RBD patients using SPECT with ^{123}I-2βcarbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane (^{123}I-FP-CIT). Two reports found decreases of striatal DAT only in a minor proportion of RBD patients: 2 out of 11[98] and 2 out of 5 patients,[81] respectively. A third study reported group comparisons between 14 idiopathic RBD patients,

14 early-stage PD patients, and 12 controls.[99] RBD patients showed a lower binding in the striatum, in particular in the putamen, compared to controls but higher when compared to PD. This result is in line with the ^{123}I-IPT SPECT studies from Eisensehr and colleagues,[94,95] and with the concept of a continuum in striatal DA impairment from RBD to PD. In a fourth, recent and longitudinal study, 43 idiopathic RBD and 18 controls were assessed for striatal DAT.[84] Reduced binding was found in 40% of RBD patients. The same study included a clinical follow-up showing the appearance of a neurodegenerative disorder (PD, dementia with Lewy bodies or multiple-system atrophy) in 8 of these patients within 2.5 years after neuroimaging. Importantly, 6 of these 8 RBD patients who would develop a neurodegenerative disease had a reduced striatal DAT at baseline. This study also associated TCS to measure echogenicity of SN (see earlier), and the combination of ^{123}I-FP-CIT SPECT and TCS allowed the detection of anomalies at baseline in all 8 RBD patients who would convert to a full-blown neurodegenerative disorder. These results suggest that ^{123}I-FP-CIT SPECT in association with TCS might constitute methods of interest in the identification of RBD patients at higher risk for the development of synucleinopathies.

A case report described the changes over time of nigrostriatal presynaptic DA function in RBD. PET using ^{11}C-carbomethoxy flurophenyl tropane (^{11}C-CFT) was acquired twice in a 73-year-old man: 1 year and 3.5 years after RBD onset, respectively.[100] While only a slight binding decrease was noted in the posterior putamen after 1 year (compared to controls), the decrease was more pronounced in the striatum after 3.5 years, with an estimate of a 4%–6% decrease per year. The progressive decrease in striatal DAT was confirmed by a prospective ^{123}I-FP-CIT SPECT study conducted in 20 idiopathic RBD patients.[101] In this study, patients were evaluated for presynaptic DA function at baseline, after 1.5 years, and again after 3 years, showing a progressive decline in striatal DAT over time.

Finally, concerning postsynaptic DA function, the two studies from Eisensehr and colleagues also included acquisitions with ^{123}I-IBZM SPECT, targeting striatal postsynaptic D2 receptor density.[94,95] No significant change was observed between RBD and other groups (controls, PD), demonstrating that postsynaptic DA function is not affected in RBD patients.

Summary

Neuroimaging findings in sleepwalking and RBD can be summarized as follows:

1. *Sleepwalking* appears as a *dissociated state*, with mixed functional brain patterns of SWS and wakefulness.
2. Structural and functional studies have demonstrated alterations in the *pons* of *RBD* patients, supporting the involvement of pontine nuclei in RBD pathophysiology.
3. Structural and functional studies suggest degenerative changes of the *SN* and presynaptic dysfunction of *DA* nigro-striatal pathways in *RBD*, which are in agreement with the hypothesis that RBD actually represents an early stage of a *neurodegenerative* disease, in particular a synucleinopathy (PD, dementia with Lewy bodies and multiple-system atrophy).
4. Neuroimaging provides objective *biomarkers* of RBD evolution towards neurodegenerative disorders, in particular with TCS, striatal DAT and hippocampal perfusion patterns.

While an increasing number of neuroimaging studies are devoted to RBD, only one study with a single patient is available in sleepwalking. Additional studies are needed to confirm and extend this study, especially as regards the role of SWS alterations in the pathophysiology of somnambulism. Neuroimaging studies have brought important support to theories suggesting a role for pontine structures and DA dysfunction in RBD. Future studies are needed to further explore the relationship between RBD and neurodegenerative diseases, and especially the evolution from RBD to full-blown neurodegenerative disorders. They should also address the role of structures such as the hippocampus in RBD, along with cognitive aspects of the disease. Finally, the investigation of brain activity patterns during behavioral episodes as well as during sleep itself should be further documented in the next neuroimaging studies of RBD.

FATAL FAMILIAL INSOMNIA

Fatal familial insomnia (FFI) is a hereditary autosomal dominant disease caused by prion-protein gene (PRNP) mutation. It is linked to a mutation of PRNP at codon 178, and to the presence of a methionine codon at position 129. Clinical features include insomnia, autonomic hyperactivity, and motor abnormalities.[102,103]

This disease is invariably lethal, hence its name.[102] The disrupted sleep profile presents a loss of sleep spindles and SWS, and enacted dreams during REM sleep.[103]

A prominent hypometabolism was observed in the anterior part of the thalamus in four patients investigated with ^{18}F-FDG PET during wakefulness.[104] Two of those patients exhibited symptoms restricted to insomnia and dysautonomia: in one subject, hypometabolism was exclusively located in the thalamus; in the other one, hypometabolism was also found in frontal, anterior cingulate, and temporal polar areas in addition to the thalamus. In the two remaining patients, who had a more complex clinical presentation, hypometabolism was more widespread and involved many cortical areas, the basal ganglia, the cerebellum, and the thalamus. This widespread pattern was found significantly aggravated as the disease progressed in one patient reexamined several months later. However, whether widespread hypometabolism is indicative of the more advanced stages of the disease or indicates a different variant of this disorder (disseminated vs. thalamic) still remains to be confirmed.

The same group then studied seven FFI patients with ^{18}F-FDG PET, to examine regional cerebral glucose utilization in FFI and its relation with neuropathology.[105] A severe decrease of glucose utilization in the thalamus and a milder decrease in the cingulate cortex were detected in all FFI patients. Six of these patients also displayed a hypometabolism of 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 longer symptom duration at the time of study. A comparison with neuropathologic data showed that areas with neuronal loss were among those that were shown hypometabolic in the PET study. However, hypometabolism extended beyond areas demonstrated by neuropathologic data, and it significantly correlated with the amount of prion protein across brain areas. Altogether these data indicate that hypometabolism of the thalamus and cingulate cortex is a common feature of FFI, while the involvement of other brain regions may depend on various factors, such as symptom duration.[105] Interestingly, thalamic hypometabolism was also found in a case of genetically confirmed FFI with atypical clinical presentation (ataxia, dementia, and dysautonomic signs, no obvious insomnia per se).[106]

Recently, an ^{18}F-FDG PET study assessed the changes in brain metabolism in carriers of the mutation involved in FFI before the actual onset of the symptoms. In one of these subjects, selective thalamic hypometabolism was detected 13 months before disease onset, suggesting that thalamic metabolic changes constitute an early, even preclinical, marker of FFI[107] (Fig. 19.2).

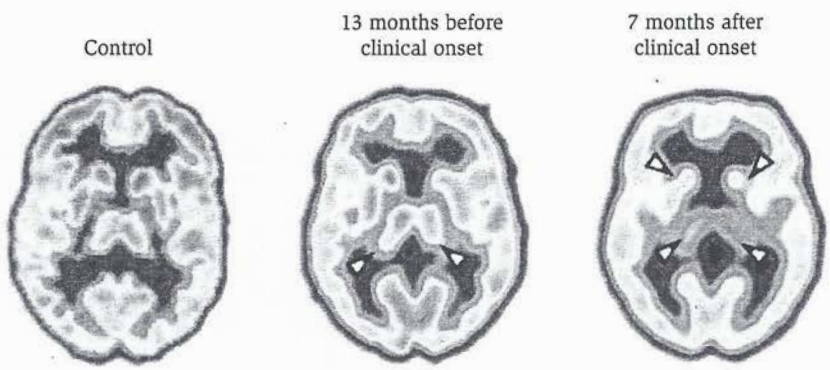

FIGURE 19.2 Brain glucose metabolism in fatal familial insomnia (FFI). Decrease of glucose metabolism in the thalamus has been consistently shown in FFI. Thalamic hypometabolism is manifest in this patient with symptomatic FFI, along with metabolic decrease in the basal ganglia (*right*), as compared to controls (*left*). A milder decrease of glucose metabolism in the thalamus was already detected in that FFI patient more than 1 year before the onset of symptoms (*middle*). This figure shows results from an ^{18}F-FDG PET study. (Reproduced from Cortelli et al.,[104] with permission.) (*See* color insert.)

This observation is highly important since the thalamus plays a key role in sleep regulation, especially in the generation of brain oscillations of sleep such as spindles.[108] Indeed, spectral analysis in the frequency band of spindles showed a reduction of spindle activity 13 months before disease onset in that patient who also exhibited a reduced thalamic metabolism at the same time.[107]

Only one imaging study investigated the changes of neurotransmission in FFI. Serotonin transporters of two FFI patients were examined with ^{123}I-β-CIT SPECT as compared to age-expected control values.[109] 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 the serotonergic neurotransmission, its eventual causative role in FFI pathophysiology still remains to be established.[109]

NOCTURNAL EPILEPSY

Nocturnal Frontal Lobe Epilepsy

Nocturnal frontal lobe epilepsy (NFLE) is a peculiar form of epilepsy with seizures arising from foci within the frontal lobe and occurring almost exclusively during sleep. Three main phenotypes can be identified within the clinical spectrum of NFLE seizures: paroxysmal arousals (PAs), defined as brief (<20 seconds) and recurrent arousals associated with a stereotypical motor activity; nocturnal paroxysmal dystonia (NPD), constituted by recurrent and longer (<2 minutes) motor attacks with dystonic or hyperkinetic features; and episodic nocturnal wanderings (ENWs), which are agitated and stereotyped behaviors resembling somnambulism.[110] Differential diagnosis might be difficult, especially with parasomnias, since epileptic activity is often not visible on standard scalp EEG recordings.[111] Vetrugno and colleagues reported a case study of one patient with a history of PA, NPD, and ENW.[112] In this patient, ^{99m}Tc-ECD SPECT was acquired twice: during an episode of PA (ictal), and during sleep (interictal) at a 1-week interval. Comparing ictal and interictal scans showed that PA was associated with increased perfusion in the cerebellum and anterior cingulate gyrus. Ictal scans in this patient were also compared with scans of 20 age-matched healthy volunteers during wake: compared to controls, the episode was still associated with hyperperfusion of cerebellum and anterior cingulate gyrus but also with a decreased perfusion of frontal and temporal associative areas. The authors interpreted this finding as reflecting a dissociative state, with the activity of anterior cingulate and cerebellum responsible for a state of behavioral arousal, and the decreased perfusion in associative frontal-temporal areas accounting for an impaired awareness during the episodes.[112] The consistency and specificity of this result still need to be confirmed. In particular, these patterns are strikingly similar to those found during a sleepwalking episode [53] and could thus be related to nonspecific central patterns common to parasomnias and seizures arising from sleep.[113] Another patient was likewise studied with ^{99m}Tc-ECD SPECT during an episode of NPD.[114] In agreement with the study on PA, this report described an increased perfusion in the anterior cingulate cortex during ictal compared with interictal scans.

NFLE can also be inherited as an autosomal dominant trait. In this case, it is termed autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). ADNFLE is associated with different mutations in the genes encoding two subunits (α4 and β2) of the neural nicotinic acetylcholine receptor (nAChR). This condition has been associated with abnormal brain activity during the interictal period (awake state) in a study using PET with ^{18}F-FDG, that is, decreased glucose uptake over the left middle and superior frontal gyri and the left central regions, including anterior parietal lobe.[115] These patterns were described in 6 members of a same Korean family compared to 14 control subjects, and they were consistent with the EEG features showing epileptiform activity over frontocentral areas. Previously another study had shown in one ADNFLE patient a left frontal hypometabolism on interictal ^{18}F-FDG PET, which was congruent with left frontopolar onset on EEG but also a focal hyperperfusion in the same area on ictal ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) SPECT.[116] In a more recent ^{18}F-FDG PET study, Picard and colleagues likewise found a frontal hypometabolism (right orbitofrontal cortex) during the interictal period (awake state) in 5 ADNFLE patients compared to 30 controls.[117] In the same study, these authors were also able to report the regional density of nAChRs using PET with ^{18}F-A-85380, a radiotracer with a high affinity for α4β2 receptors. Comparing eight patients and seven controls, they found that ADNFLE was associated with a lower nAChR

density in the right dorsolateral prefontal cortex—in agreement with the frontal origin of this epilepsy—and with a higher density in the mesencephalon and cerebellum (Fig. 19.3). The exact significance of these localized increases in nAChR density remains unclear, but they seem to indicate an overactivated brainstem ascending cholinergic system.[117]

Benign Epilepsy of Childhood with Centrotemporal Spikes

Benign epilepsy of childhood with centrotemporal spikes (BECTS) or benign rolandic epilepsy is an idiopathic localization-related epilepsy of childhood with no recognized underlying cause other than a possible hereditary predisposition. Seizures are typically nocturnal and confined to sleep and are accompanied by abnormal motor movement, including the face, the leg, or the full body. Structural imaging studies (CT scans and MRI) have shown that brain lesions can be found in approximately 15% of patients with BECTS (e.g., enlargement of ventricles or hippocampal atrophy).[118] This association seems to be coincidental, since the presence of such lesions did not affect the prognosis of the disease. More recently, a study using anatomical MRI has confirmed the high prevalence of abnormal findings in BECTS: more than 40% of patients had lesions such as hippocampal atrophy, malformation of cortical development, or Chiari malformation.[119] These lesions were still of unclear clinical significance. Functional imaging remains to be systematically studied in patients with BECTS.

Landau-Kleffner Syndrome and Syndrome of Continuous Spike-and-Wave Discharges during Slow-Wave Sleep

The Landau-Kleffner syndrome (LKS) and the syndrome of continuous spike-and-wave discharges during SWS (CSWS) have been originally described and are still considered separately. LKS is characterized by acquired aphasia and paroxysmal sleep-activated EEG predominating over the temporal or parietal-occipital regions.[120] Paroxysmal events are spike-and-wave discharges that are activated by SWS. Secondary symptoms include psychomotor or behavioral disturbances. LKS has a favorable outcome for seizure control.[121] CSWS is characterized by continuous spike-and wave discharges during SWS, usually combined with global intellectual deterioration and epileptic seizures.[122] These two syndromes share many features in common, including early onset during childhood, deterioration of cognitive function (previously acquired normally), seizure type, EEG pattern, and pharmacological reactivity. They have also in common the regression of neuropsychological symptoms, EEG abnormalities, and seizures before the end of adolescence. Structural lesions evaluated by CT scan or MRI are usually absent or nonspecific.[121–124]

In both conditions, initial functional neuroimaging studies using PET[121,125–128] and SPECT[127,129–135] described metabolic abnormalities that predominantly involved the temporal lobes. Focal or regional areas of decreased and increased metabolism were reported. A normal distribution of cerebrospinal fluid was reported in one isolated case.[136] These early results were difficult to interpret in terms of pathogenesis.

In a restrospective analysis of ^{18}F-FDG PET data during sleep and wakefulness in a population of patients with CSWS, regional increases and decreases in cerebral glucose metabolism were again observed.[137] The metabolic patterns were found to be variable from one patient to another and grossly related to the neuropsychological deterioration. Moreover, metabolic patterns in individual patients were reported to change over time. Four basic metabolic characteristics were drawn up from this study. First, patients with CSWS have a higher rate of metabolism in the cortical mantle than in the thalamic nuclei. This metabolic pattern is characteristic of an immature brain. Second, they show focal or regional metabolic abnormalities of the cortex, suggesting a focal origin of the spike-and-wave discharges. Third, they have metabolic disturbances predominantly involving associative cortices, compatible with a deterioration of cognitive functions. Fourth, glucose metabolism in thalamic nuclei remains symmetrical despite significant cortical asymmetries, suggesting that corticothalamic neurons either do not participate in the generation of spike-and-wave discharges or are being inhibited by pathological mechanisms.

More recently, voxel-based analyses of cerebral glucose metabolism were performed in a group of 18 children with CSWS.[138] Each patient was compared with a control group and the influence of age, epileptic activity, and corticosteroid treatment on metabolic

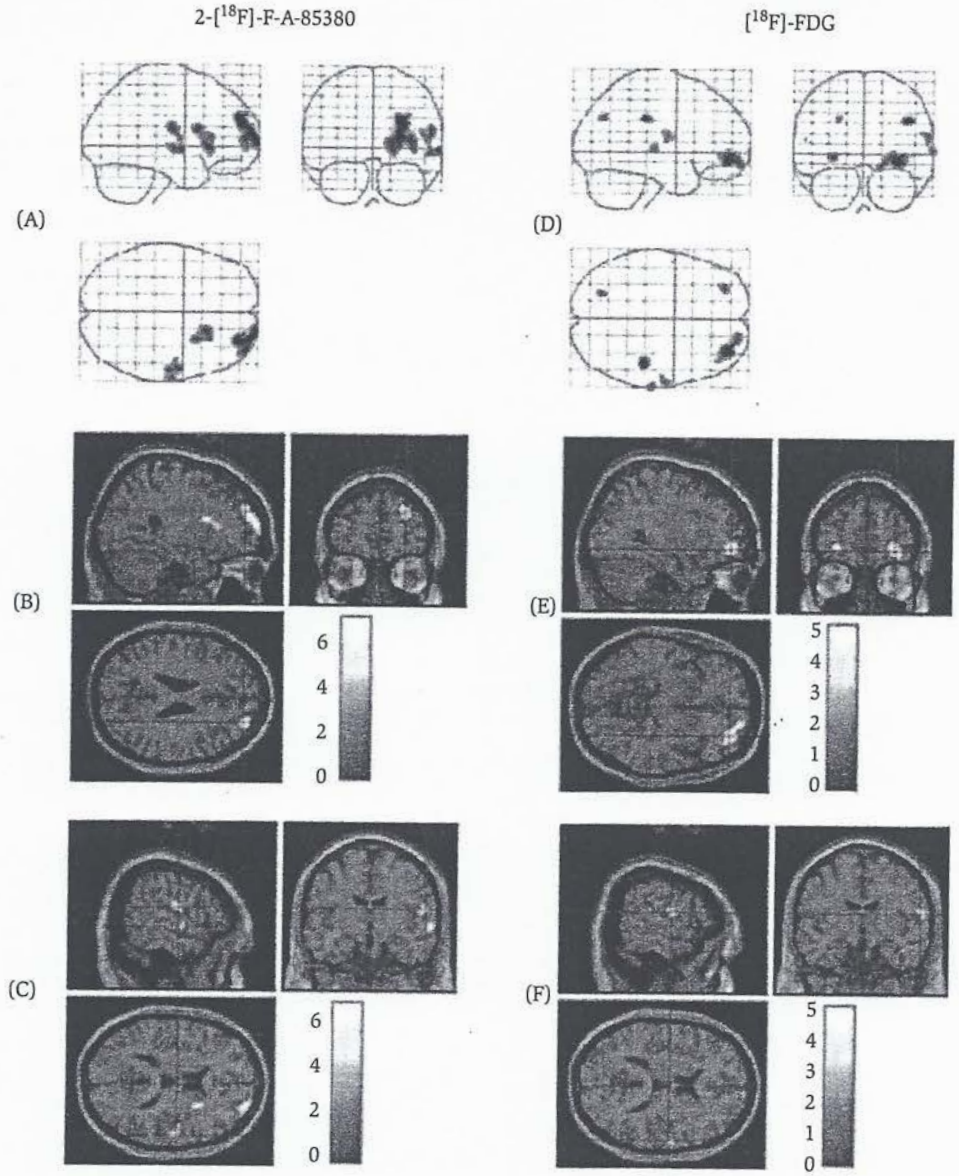

FIGURE 19.3 Brain glucose metabolism and nicotinic acetycholine receptor density in autosomal dominant nocturnal frontal lobe epilepsy. The right panels (*D–F*) illustrate the decrease of glucose metabolism in the right prefrontal region (*E*) and right opercular cortex (*F*), in ADNFLE as compared to controls, during the interictal period (^{18}F-FDG PET study). Given that ADNFLE is associated with mutations in the genes encoding subunits α4 and β2 of nAChR, the brain regional density of nAChR has also been investigated. As shown in the left panels (*A–C*), ADNFLE is associated with a lower nAChR density in the right prefontal region (*B*) and right opercular cortex (*C*), as compared to controls (^{18}F-A-85380 PET study). Note the similarity between glucose metabolism and nAChR distributions, both of which being in agreement with the frontal origin of ADNFLE. (Reproduced from Picard et al.,[114] with permission.) (*See* color insert.)

abnormalities was assessed. Cerebral metabolic patterns were heterogeneous across patients with CSWS. Age and intensity of interictal spiking did not significantly differ in patients showing focal hypermetabolism compared with the other ones. Treatment with corticosteroids corrected focal hypermetabolism. Altered parietofrontal connectivity observed in patients with hypermetabolism was interpreted as a phenomenon of remote inhibition of the frontal lobes induced by highly epileptogenic and hypermetabolic posterior cortex.

Altogether these studies suggest that CSWS is produced by an alteration in the maturation of one or more associative cortices, potentially leading to disturbed neuronal wiring. An imbalance of inhibitory and excitatory drives would lead to a deterioration of associated higher cerebral functions and would create conditions favorable for the generation of neuronal discharges. Epileptic discharges would be triggered during SWS because of the physiological reinforced synchronization of neuronal firing characteristic of SWS.[139]

CONCLUSION

Neuroimaging has brought an important contribution to sleep medicine, and especially to the topic of movements disorders in sleep. The development of techniques and methods of analysis has allowed an increasing number of complex neuroimaging studies to emerge. The systematic study of anatomical changes in both gray and white matter has allowed, for instance, the detection of subtle structural changes in key structures for RBD pathogenesis.[73] Recent ligand studies were able to confirm the existence of striatal DA dysfunction in RLS.[39] The identification of brain regions involved in the generation of paroxysmal episodes in nocturnal epilepsy was made possible by brain metabolism studies.[112,117] Future studies will further explore the patterns of brain function predictive of clinical evolution, as well as the neuroimaging longitudinal changes in the course of disease progression. This is illustrated, for example, by the relationship between neuroimaging data at baseline and clinical progression of RBD toward neurodegenerative disorders.[84,87] Beyond the understanding of pathophysiology, neuroimaging techniques also constitute promising tools for the diagnostic and prognostic evaluation of sleep-related movement disorders.

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