Rapid-Eye-Movement Sleep Behavior Disorder

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This book is dedicated to Michel Jouvet, M.D., PhD, pioneer in the first experimental animal model of Rapid-Eye-Movement Sleep Behavior Disorder (RBD), reported in 1965, and to Mark W. Mahowald, M.D., pioneer in the discovery of RBD in humans, reported in 1986.

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(November 16, 1925–October 3, 2017)
Professor of Experimental Medicine
Université Claude Bernard Lyon, France
Pioneer in the first experimental animal model of RBD, 1965

Mark W. Mahowald, M.D.
Director, Minnesota Regional Sleep Disorders Center (1982–2010)
Professor of Neurology, University of Minnesota Medical School (retired)
Pioneer in the discovery of RBD in humans, 1986

Preface: RBD in a Nutshell and Suggested Ways to Read This Book

RBD in a Nutshell

Rapid-eye-movement (REM) sleep behavior disorder (RBD) is a parasomnia (sleep behavioral and experiential disorder) that consists of abnormal behavioral release during REM sleep with loss of the mammalian skeletal muscle paralysis of REM sleep, "REM-atonia" [1]. RBD is the only parasomnia that requires objective polysomnographic (PSG) confirmation [1]. The PSG hallmark of RBD consists of electromyographic abnormalities during REM sleep, "loss of REM-atonia" or "REM-without-atonia" (RWA), with increased muscle tone and/or increased phasic muscle twitching. RBD represents how one of the defining features of mammalian REM sleep, viz. REM-atonia, can become severely impaired, allowing for clinically consequential behavioral release during REM sleep. A person with RBD moves with eyes closed while attending to the inner dream environment and being completely unaware of the actual bedside surroundings, a highly vulnerable state that poses a risk for serious injury [2].

The behavioral release during REM sleep often involves the acting-out of dreams that are confrontational, aggressive, and violent, and which commonly result in injuries to self or bed partner, thus triggering clinical evaluation and treatment [3]. The enacted dreams usually contain unfamiliar people and animals, and the dreamer is rarely the primary aggressor and often is defending himself or spouse. The reported dream action (after an awakening) closely matches the observed behaviors during video-PSG evaluation. RBD is a dream disorder almost as much as it is a behavioral disorder of sleep, which raises intriguing questions about a common pathophysiology underlying the linked emergence of closely matching abnormal behaviors and abnormal dreams in RBD—and also underlying the shared pharmacologic benefit with conjoint control of the abnormal behaviors and dreams with the same therapy (usually clonazepam taken at bedtime) [3]. Furthermore, a still insufficiently investigated, but ubiquitous, phenomenon in RBD is the minor jerking of the extremities during REM sleep [4]. One school of thought from basic research suggests that "an interpretation of RBD that focuses increased attention on the brainstem as a source of the pathological movements and that considers sensory feedback from moving limbs as an important influence on the content of dream mentation" should be pursued [5].

The traditional RBD clinical profile involves middle aged and older men with violent and injurious dream-enacting behaviors [3], and with >80% of these patients eventually developing a parkinsonian (α-synucleinopathy) neurodegenerative disorder, usually Parkinson's disease (PD) or dementia with Lewy bodies (DLB), with a mean interval from RBD onset to overt neurodegeneration being in the 12–14 year range [6, 7]. These striking findings have forced a reconsideration in current thinking insofar as RBD should now be considered prodromal parkinsonism, and thus what originally was called "idiopathic RBD" should now be called "isolated RBD," which implies the eventual transformation of the isolated clinical RBD state to overt parkinsonism with RBD [4]. This very close association has spurred major research efforts to develop and test neuroprotective/disease-modifying agents in patients with isolated RBD in an effort to slow down or halt progression to overt neurodegeneration, as discussed in Chaps. 3 and 45.

The traditional clinical profile of RBD, viz. predominantly involving middle aged and older men with aggressive dream-enacting behaviors, will now need to be reconsidered, given a recent population-based study of middle aged to older adults with PSG confirmation of RBD that found a 1.06% prevalence of RBD—and with gender parity [8]. Since women generally have less aggressive and injurious RBD, they present for medical attention much less frequently than men. Therefore, the traditional RBD profile has reflected a clinical referral bias on account of more aggressive and injurious RBD behaviors in men compared to women. However, once a promising neuroprotective agent becomes available, then a concerted effort must be initiated to find the women with RBD who had not sought medical attention (along with men having mild RBD), since it is the presence of RWA/RBD, and not its severity, that carries the strong risk for future parkinsonism. This effort would entail collaboration with geriatric medicine, geriatric psychiatry, primary care, and neurology clinics. Also, the 1.06% RBD prevalence found in this study is the first PSG-confirmed prevalence of RBD in the general population [8], and so RBD is not an uncommon disease, with a prevalence comparable to that of schizophrenia.

Therefore, millions of people around the world have RBD—and especially RBD as prodromal parkinsonism or dementia. There has been growing research devoted to identifying the clinical and biomarker profiles of the highest-risk idiopathic/isolated RBD patients for imminent conversion to overt synucleinopathy within 5 years, as these would be the ideal candidates for inclusion in neuroprotective trials. In this research context, special recognition should be given to the outstanding and prodigious body of RBD work of Jacques Montplaisir, leader of the Montreal group that is well represented in this book by J-F Gagnon with Chap. 34 on neuropsychologic aspects of RBD and by Ron Postuma with Chap. 36 on RBD biomarkers.

The phenotype of RBD in patients under 50 years of age has recently been recognized to differ from the traditional RBD phenotype of middle aged/older men with aggressive RBD behaviors, as covered in Chap. 15. Younger RBD patients have greater gender parity, less severe RBD, greater association with narcolepsy-cataplexy (narcolepsy type 1; Chap. 11), greater association with psychiatric disorders and with antidepressant use, greater association with the parasomnia overlap disorder (POD:

RBD + NREM sleep parasomnia [sleepwalking, sleep terrors] [1]; the topic of Chap. 27), and perhaps also greater association with autoimmune diseases. RBD in children and adolescents, although rare, is usually associated with narcolepsy type 1, POD, and brainstem tumors, as discussed in Chap. 14. Most antidepressant medications (especially SSRIs, venlafaxine, and tricyclic antidepressants) can trigger or aggravate RBD, but not bupropion, a dopaminergic-noradrenergic agent, as discussed in Chap. 10. Finally, acute RBD exists and emerges in the context of acute toxic-metabolic disturbances and acute drug withdrawal states, as discussed in Chap. 12.

The differential diagnosis of RBD with dream enactment (i.e., the RBD mimics) includes NREM sleep parasomnias (sleepwalking, sleep terrors), obstructive sleep apnea ("OSA pseudo-RBD"), periodic limb movement disorder ("PLM pseudo-RBD"), and nocturnal seizures, as discussed in Chap. 26.

Pharmacotherapy of RBD is highly effective in most reported cases, with benefit achieved from bedtime clonazepam and/or melatonin therapy in controlling the problematic behaviors and associated dreams, i.e., the presenting clinical complaints. The mechanism of action for these medications is currently unknown. Chapters 24 and 25 discuss the therapies of RBD.

Animal models of RBD that closely resemble human RBD have been developed since 1965, i.e., since 21 years before RBD was formally recognized in humans [3]. Most animal models involve experimental lesions to the pontine and medullary centers responsible for generating REM-atonia in cats, rats, and mice. There is also a transgenic mouse model of RBD in mice deficient in glycine and GABA neurotransmission [9]. These animal models offer the hope of not only better understanding the pathophysiological mechanisms underlying human RBD but also better understanding the pathogenesis of RBD in α-synucleinopathy neurodegenerative disorders, and help pave the way for developing neuroprotective agents. Also, not surprisingly, RBD has been found in virtually all categories of neurologic disorders, and with different classes of medications, since any lesion or neurotransmitter/pharmacologic disruption to the brainstem centers and pathways subserving REM-atonia [10] can result in RBD.

To conclude, RBD epitomizes the dynamic cross-fertilization of clinical and basic science and is a premier example of the critical role of animal experimentation in clinical (sleep) medicine, and especially in RBD [11], as demonstrated in this book—the first RBD textbook.

Suggested Ways to Read This Book

As shown in the Table of Contents, the 45 chapters in this book are grouped into six parts that serve as important initial signposts for the material being presented and discussed. The readers can then browse and read their way through the book as they wish. Virtually all the chapters were written by internationally recognized leaders in the RBD topics covered in their chapters. In other words, the readers will hear "first-hand news" about RBD.

I would also encourage another way to read this book, for either scientific pursuit, clinical information, teaching purposes, or personal interest. I present below 11 modules of chapter groupings to encourage readers to delve into areas of greatest interest or greatest curiosity. These modules should also facilitate group discussions in teaching settings, and to motivate or deepen interest in pursuing more knowledge on RBD-related topics. Table 1 contains an astounding 46 clinical and basic science research areas that intersect with RBD, and the number of research areas linked with RBD will continue to grow, including new areas of interlinked research. As I have written, RBD is situated at a strategic and busy crossroads of sleep medicine, neurology, and the clinical and basic neurosciences [12]. New clinical disorders are being identified with RBD as one of the core features—for example the fascinating anti-IgLON5 disease discussed at length in Chap. 8 by Alex Iranzo from Barcelona, a member of the discovery group. Also, an established neurologic disorder, such as dementia with Lewy bodies, now has RBD as one of its core diagnostic criteria, as discussed in Chap. 6 by Bradley Boeve.

It is noteworthy that Module V (RBD and Neurodegeneration) contains nine chapters, whereas the other ten modules contain two to five chapters each. The area of RBD and neurodegeneration is the preeminent "hot topic" in RBD clinical and basic science research. In fact, as discussed above, RBD is now regarded as "prodromal parkinsonism," a "Lewy body disease," with Lewy bodies being a core part of the α-synuclein pathology that is the hallmark of PD and DLB. "RBD is the disorder that precedes and continues through most of these prodromal DLB cognitive and neuropsychiatric syndromes" (Boeve, Chap. 6). RBD is the "bearer of bad tidings in PD," as it usually signals a more widespread and severe form of PD compared to PD without RBD [13]. Therefore, prodromal RBD [4] can be considered as "a double bad sign" of not only future synucleinopathy neurodegeneration, but also a more severe form of that neurodegeneration, at least in regard to PD. An urgent question posed by RBD as prodromal parkinsonism is: when, where, and how does Lewy body disease first make its appearance in the brain? [4, 14, 15].

Nevertheless, as shown in Fig. 1 (schematic diagram), a broad array of clinical insults can disturb the integrity of REM-atonia (the keeper of bodily peace during REM sleep), either singly or in combination (i.e., at one point in time, or over the course of a lifetime), to result in RWA and RBD. This puts a spotlight on how RBD can emerge with either one "big hit" (major clinical insult, e.g., stroke) or from the succession of multiple "smaller hits" (due to various types of insults) over a lifetime that eventually will overwhelm REM-atonia to trigger RWA and RBD (analogous to radiation exposure, with immediate or later onset radiation sickness). Abnormal developmental neuromotor events (in utero and early postnatal life) could become predisposing factors for future RWA/RBD, as discussed in Chap. 14. It should be evident that REM-atonia is a highly vulnerable biological entity, which puts a premium on its protection, and prevention or containment of risk factors, during the entire life cycle. For example, the effect (if any) on REM-atonia should be tested during the development of new neuroactive and psychotropic medications—and this strategy could even fortuitously yield insights into how REM-atonia could be strengthened and protected from insults to its integrity.

Finally, the 11 modules below contain the following groupings: experiential features of RBD; screening, diagnosis, and video-PSG findings in RBD; RBD across

Table 1 46 Areas of research intersecting with RBD

Basic Science Research
Neurophysiology (including REM sleep circuits)
Immunology/autoimmunity
α-synuclein/α-synucleinopathy
Developmental neurobiology
Animal models
Clinical Science Research: Neurology
Neurodegenerative disorders
Dementia (including dementia with Lewy bodies)
Parkinson's disease
Narcolepsy-cataplexy
Anti-IgLON5 disease
Neurological disorders
Electromyography
EEG/evoked potentials
Brain imaging
Autonomic nervous system
Gait and posture
Speech and voice
Eye movements
Neuroprotection
Biomarkers
Neuropathology
Clinical Science Research: Psychology/Psychiatry
Psychology
Neuropsychology
Human behavior
Depression, anxiety
Antidepressants
Benzodiazepines
Geriatric psychiatry
Impulse dyscontrol
Aggression and violence
Clinical Science Research: Sleep and Circadian Rhythms
Dreams
REM sleep
Parasomnias (REM and NREM)
Sleep-related injury/sleep violence
Sleeptalking
Melatonin
Circadian rhythms
Clinical Science Research: Other Fields
Genetics
Gender
Microbiome
Quality of life
Research design
Epidemiology (including screening instruments)
Wearable technology and smartphones
Forensic sleep medicine
Physical medicine and rehabilitation

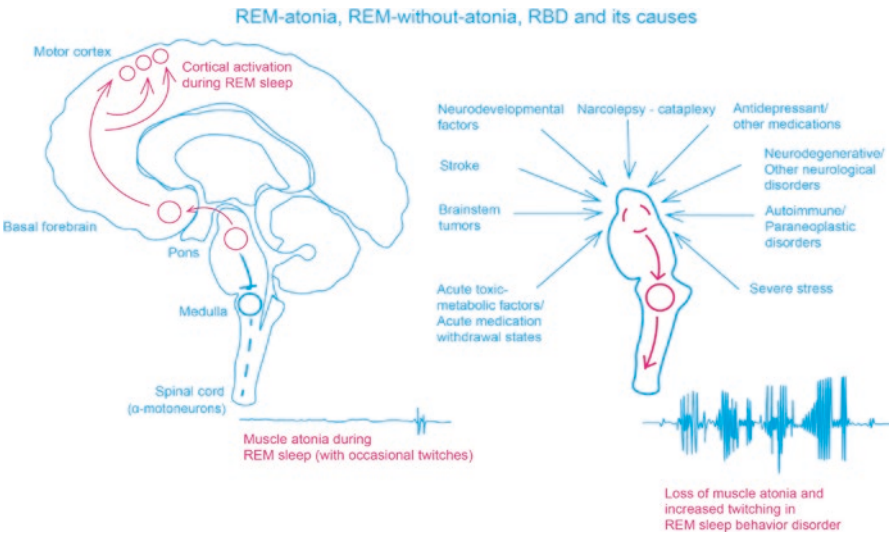

Fig. 1 Schematic diagram depicting how on the left side the pons, the site for generating REM sleep, simultaneously sends ascending activating signals (in red) to the motor cortex, and descending inhibitory signals (in blue) to the spinal cord alpha-motoneurons via the medulla, to result in REM-atonia, with brief, benign twitches in REM sleep. The right side depicts the range of clinical insults (including presumed neurodevelopmental priming in some cases) that can cause REM-without-atonia, increased twitching in REM sleep, and RBD, with disinhibition of the REM-atonia pathway indicated by the red color replacing the blue color on the left side. [The specific neuronal groups and pathways underlying this schematic diagram are contained in Chaps. 39, 42, and 43]. [Original art courtesy of I.E. Wong Fong Sang, MSc Biomedical Sciences/Neurosciences; PhD candidate in Neurobiology (expected completion in September 2018), Johannes Gutenberg University, Mainz, Germany]

the life cycle; management of RBD; RBD and neurodegeneration; RBD and the autonomic nervous system; neuropsychiatry of RBD; secondary RBD; RBD overlap disorder, mixed states, acute states; physiological underpinnings of RBD; RBD: past, present, future.

Module I (Experiential Features of RBD)

Chapter 2. The Human Dimension of RBD
Chapter 17. RBD: A Window into the Dreaming Process

Module II (Screening, Diagnosis, and Video-PSG Findings in RBD)

Chapter 18. Diagnosis of RBD
Chapter 31. The Electromyographic Diagnosis of REM Sleep Without Atonia and RBD
Chapter 20. Selective Polysomnographic Findings in REM Sleep Behavior Disorder (RBD) and Parkinson's Disease
Chapter 21. Video Analysis of Behaviors and Movements in RBD

Chapter 19. Instruments for Screening, Diagnosis and Assessment of RBD Severity and Monitoring Treatment Outcome

Module III (RBD Across the Life Cycle)

Chapter 4. Clinical Aspects of Idiopathic RBD
Chapter 15. RBD in Adults Under 50 Years Old
Chapter 16. RBD: Gender Implications
Chapter 14. RBD in Childhood and Adolescence

Module IV (Management of RBD)

Chapter 23. Management of a Patient with RBD
Chapter 24. Melatonin Therapy of RBD
Chapter 25. Clonazepam and Other Therapies of RBD
Chapter 22. Clinical Vignettes: Illustrative, Unusual, and Challenging RBD Cases
Chapter 26. Differential Diagnosis and Related Disorders: RBD Mimics

Module V (RBD and Neurodegeneration)

Chapter 5. RBD Associated with Parkinson's Disease and Multiple System Atrophy
Chapter 6. REM Sleep Behavior Disorder Associated with Dementia with Lewy Bodies
Chapter 7. RBD and Non-synuclein Neurodegenerative Disorders: A Critical Appraisal
Chapter 30. Brain Imaging of RBD
Chapter 40. Neuropathology of REM Sleep Behavior Disorder
Chapter 41. Genetics of REM Sleep Behavior Disorder
Chapter 38. Gait and Postural Disorders in RBD
Chapter 36. Biomarkers of Neurodegenerative Disease in Idiopathic RBD
Chapter 43. REM Sleep Behavior Disorder: The Link Between Synucleinopathies and REM Sleep Circuits

Module VI (RBD and the Autonomic Nervous System)

Chapter 32. RBD and the Autonomic Nervous System
Chapter 33. Cardiac Scintigraphy in RBD
Chapter 37. RBD, Gastric Peptides, and Gastric Motility

Module VII (Neuropsychiatry of RBD)

Chapter 10. RBD, Antidepressant Medications, and Psychiatric Disorders
Chapter 35. Neuropsychological Aspects: Impulse Control Disorders and Other Neuropsychiatric Features in RBD
Chapter 34. Neuropsychological Aspects: Cognition in RBD

Module VIII (Secondary RBD)

Chapter 9. Lesional RBD
Chapter 11. RBD in Narcolepsy
Chapter 8. RBD Associated with Paraneoplastic Neurological Syndromes and Autoimmune Disorders

Module IX (RBD Overlap Disorder, Mixed States, Acute States)

Chapter 27. Parasomnia Overlap Disorder: RBD and NREM Sleep Parasomnias
Chapter 28. Status Dissociatus and Its Relation to RBD
Chapter 12. Secondary RBD: Acute REM Sleep Behavior Disorder

Module X (Physiological Underpinnings of RBD)

Chapter 39. Neural Circuitry Regulating REM Sleep and Its Implication in REM Sleep Behavior Disorder
Chapter 29. Local Cortical Activations During REM Sleep and Implications for RBD
Chapter 13. Physiological Substrates of RBD Subtypes
Chapter 42. Animal Models of RBD

Module XI (RBD: Past, Present, Future)

Chapter 1. RBD: Historical Perspective
Chapter 3. The Foundation of the International RBD Study Group (IRBDSG)
Chapter 44. Toward Disease Modification Trials in RBD: Challenges and Opportunities
Chapter 45. RBD: Future Directions in Research and Clinical Care and Counseling

To conclude, the presentation of 45 chapters on RBD (grouped into 6 sections in the Table of Contents, and also grouped into 11 modules), and the presentation of 46 research areas intersecting with RBD in Table 1 should accelerate clinical, research, and educational interest in RBD, its comorbidities, and its scientific importance. These points are emphasized in a recent review article written by RBD experts [16].

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Contents

Part I

Introduction

RBD: Historical Perspective

1

Carlos H. Schenck

1.1 Introduction

The historical perspective on RBD encompasses (1) the formal discovery of RBD in 1986 and the early clinical RBD milestones, (2) the clinical historical background from 1966 to 1985, (3) the first experimental animal model of RBD from 1965, and (4) RBD described in classic literature and film.

1.2 Formal Discovery of RBD

The first report on RBD was published in 1986 in *Sleep*: "Chronic behavioral disorders of human REM sleep: a new category of parasomnia" [1]. The abstract read as follows:

> Four men, aged 67–72 years, had 4-month to 6-year histories of injuring themselves or their spouses with aggressive behaviors during sleep, often during attempted dream enactment. A 60-year-old woman had disruptive though nonviolent sleep and dream behaviors. Polysomnography did not detect seizures but did document REM sleep pathology with variable loss of chin atonia, extraordinarily increased limb-twitch activity, and increased REM ocular activity and density. A broad range of REM sleep behaviors was recorded on videotape, including stereotypical hand motions, reaching and searching gestures, punches, kicks, and verified dream movements. Stage 3–4 slow wave sleep was elevated for age in all patients. NREM sleep was devoid of harmful behaviors, although three men had periodic myoclonus. There was no associated psychiatric disorder, whereas serious neurologic disorder was closely associated in four cases: olivo-ponto-cerebellar degeneration, Guillain-Barré syndrome, subarachnoid hemorrhage, and an atypical dementia. Two patients had immediate and lasting sleep behavioral suppression induced by clonazepam, and another

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patient had the same response with desipramine. All instances of drug discontinuation prompted immediate relapse. In four cases there was associated dream hyperactivity, which resolved with behavioral control. These REM sleep neurobehavioral disorders constitute another category of parasomnia, replicate findings from 21 years ago in cats receiving pontine tegmental lesions, and offer additional perspectives on human behavior, neurophysiology, pharmacology, and dream phenomenology.

Despite the variable loss of the customary, generalized muscle paralysis of REM sleep ("REM atonia"), all other major features of REM sleep remain intact in RBD, such as REM sleep latency, REM sleep percent of total sleep time, number of REM sleep periods, and REM/NREM sleep cycling.

The discovery of RBD was described in the book *Paradox Lost: Midnight in the Battleground of Sleep and Dreams* [2]. I had just become a member of the Minnesota Regional Sleep Disorders Center. On my first day evaluating patients, September 11, 1982, the second patient on my schedule was a Mr. Donald Dorff, who complained of "physical moving dreams" and "violent moving nightmares." As described by Michael Long at the start of his story in the December 1987 issue of *National Geographic* magazine ("What Is This Thing Called Sleep?"), "The crowd roared as running back Donald Dorff, age 67, took the pitch from his quarterback and accelerated smoothly across the artificial turf. As Dorff braked and pivoted to cut back over tackle, a huge defensive lineman loomed in his path. One hundred twenty pounds of pluck, Dorff did not hesitate. But let the retired grocery merchandiser from Golden Valley, Minnesota, tell it: 'There was a 280-pound tackle waiting for me, so I decided to give him my shoulder. When I came to, I was on the floor in my bedroom. I had smashed into the dresser and knocked everything off it and broke the mirror and just made one heck of a mess. It was 1:30 a.m.'"

Mr. Dorff had been acting out his dreams for several years, and after his doctor had found nothing medically wrong with him, nor had a psychiatrist found anything mentally wrong, he was referred to our sleep center. On September 16, 1982, 5 days after I had evaluated Mr. Dorff, he was studied in our sleep laboratory. During each of his apparent REM sleep periods, there were many jerks and twitches and sometimes more elaborate and violent behaviors that correlated with the dreams that he reported when he woke up. However, confirmation that these were truly REM sleep events came at daybreak. As I wrote, "The next morning, in reviewing Don Dorff's polygraphic sleep tracings and videotaped behaviors, Mark Mahowald, M.D. and Andrea Patterson, R.PSGT & R.EEGT, our sleep center director and our sleep laboratory manager and chief technologist, repeatedly challenged each other, going back and forth in playing 'Devil's advocate.' The question was whether Don's violent dream-enacting activity had occurred during REM sleep… So kudos to Mark and Andrea, who jointly discovered the polygraphic foundation of REM sleep behavior disorder-RBD" [2].

1.3 Early Clinical RBD Milestones

RBD was named in our second report published in *JAMA* in 1987 [3], and among the ten patients in the original series, five had diverse neurologic disorders etiologically linked with RBD, and five were idiopathic [1, 3]. As a larger group of

idiopathic RBD (iRBD) patients was gathered and followed longitudinally at our center, a surprisingly strong and specific association with eventual parkinsonism and dementia became apparent, with our first report published in 1996 (and extended to 2013) [4, 5]. Other early RBD clinical milestones from our center include RBD in the differential diagnosis of sleep-related injury [6]; forensic aspects of RBD [7], later updated to include "parasomnia pseudo-suicide" [8]); status dissociatus (with emergence of RBD behaviors during indeterminate EEG/ Polysomnographic (PSG) states) [9]; RBD affecting patients in intensive care units [10]; antidepressant medication-induced RBD [11]; RBD associated with narcolepsy-cataplexy [12]; association of RBD with specific HLA haplotypes [13]; and the parasomnia overlap disorder (RBD with NREM parasomnias) [14]. RBD has been included in each edition of the International Classification of Sleep Disorders, including the current 3rd edition [15]. A 16-year perspective on RBD was published in *Sleep* for its silver anniversary issue in 2002 [16]. Furthermore, the jerks, twitches, movements, and behaviors of RBD may represent the pathological reemergence of primordial ontogenetic and phylogenetic motor activity patterns [17].

The August 2013 issue of *Sleep Medicine* was devoted to RBD, with 18 peer-reviewed papers covering basic and clinical sciences and both original research and review articles. The Preface described how "RBD is situated at a strategic and busy crossroads of sleep medicine and the neurosciences. RBD offers great breadth and depth of research opportunities, including extensive inter-disciplinary and multinational research opportunities" [18]. The Preface to this book expands on these statements by listing and commenting on the large number of diverse research areas intersecting with RBD that provide many future interdisciplinary research opportunities. The "RBD odyssey" exemplifies the strong cross-linkage between the RBD basic and clinical sciences [19].

Finally, in 1987 a documentary film on RBD was produced at our sleep center, "Rapid Eye Movement Sleep Behavior Disorder" [20]. This film is contained in the archives at The National Library of Medicine, Department of Health and Human Services, Public Health Service, National Institute of Health (NIH), Bethesda, Maryland.

1.4 Clinical Historical Background of RBD: 1966–1985

Various PSG and clinical aspects of correlates of chronic and acute human RBD (as we now call it) were described since 1966 by investigators from Japan, Europe, and North America, almost exclusively in neurologic and drug intoxication/withdrawal settings, as reviewed [1, 16, 21, 22], and as discussed in Chap. 12. Two groups of pioneering investigators should especially be recognized, as reviewed [16]: (1) Passouant et al. from France in 1972 first identified a dissociated state of REM sleep with tonic muscle activity induced by tricyclic antidepressant medication. (2) Tachibana et al. from Japan in 1975 named "stage 1-REM sleep" as a peculiar sleep stage characterized by muscle tone during an REM sleep-like state that emerged during acute psychoses related to alcohol and meprobamate abuse [23]. Also, clomipramine therapy of cataplexy in a group of patients with narcolepsy commonly

induced REM without atonia (RWA) in a 1976 study [24]. Elements of both acute and chronic RBD manifesting with "oneirism" were represented in the early literature, along with isolated RWA: delirium tremens (DTs) and other sedative and narcotic withdrawal states, anticholinergic use, spinocerebellar and other brainstem neurodegenerative disorders, and brainstem tumor [25] . The "REM rebound and REM intrusion" theories were proposed and discussed in many of these early reports. Finally, the 1986 report in *Sleep* firmly established that RBD is a distinct parasomnia that occurs during unequivocal REM sleep and which can be either idiopathic or symptomatic of a neurologic disorder [1]. PSG monitoring of these patients established that RBD did not emerge from a "stage-1 REM sleep" that was distinct from REM sleep, nor did RBD emerge from a poorly defined variant of REM sleep, nor from an unknown or "peculiar" stage of sleep, nor during "delirious" awakenings from sleep—all of which had been mentioned in the prior literature.

1.5 Experimental Animal Model of RBD

An experimental animal model of RBD was first reported in 1965 by Jouvet and Delorme from Lyons [16], with subsequent work on the model by Morrison and colleagues at the University of Pennsylvania beginning in the early 1970s [16]. Lesions in the peri-locus ceruleus area released a spectrum of "oneiric" behaviors during REM sleep (also called paradoxical sleep). These oneiric behaviors in cats closely match the repertoire of RBD behaviors in humans. Chapters 42 and 43 discuss the animal models of RBD in cats, rats, and mice. A therapeutic animal-human circle is completed with RBD. There is the historical progression from an experimental animal model of RBD shedding light on human RBD, which in turn has encouraged better recognition and management of RBD affecting cats and dogs presenting to veterinary clinics with violent sleep behaviors [16, 26].

1.6 RBD Described in Classic Literature and Film

Miguel de Cervantes described RBD in *Don Quixote* more than 400 years ago, in 1605: "He was thrusting his sword in all directions, speaking out loud as if he were actually fighting a giant. And the strange thing was that he did not have his eyes open, because he was asleep and dreaming that he was battling the giant… He had stabbed the wine skins so many times, believing that he was stabbing the giant, that the entire room was filled with wine" (Cap. XXXV *Aventura De Los Cueros De Vino*). Furthermore, there is strong suggestive evidence from a careful reading of *Don Quixote* that he also suffered from dementia with Lewy bodies (DLB) with fluctuating cognitive decline, complex visual and auditory hallucinations, and paranoid delusions [27]. (Chap. 6 discusses the strong link of RBD with DLB). Finally, the eighteenth-century philosopher Immanuel Kant may have suffered from combined DLB-RBD as manifestations of his 8-year terminal neurological illness [28].

RBD was depicted in Disney animated films long before the formal identification of RBD in humans in 1986 [29]. In *Cinderella* (1950), a dog had nightmares with dream enactment, and three additional dogs with presumed RBD appeared in *Lady and the Tramp* (1955), *The Fox and the Hound* (1981), and in the short film *Pluto's Judgment Day* (1935). These dogs were elderly males who would pant, whine, snuffle, howl, laugh, paddle, kick, and propel themselves while dreaming that they were chasing someone or running away. Moreover, in *Lady and the Tramp*, the dog was also losing his sense of smell and his memory, two prominent associated features of human RBD as an evolving neurodegenerative disorder. The Disney screenwriters were astute observers of sleep and its disorders, including RBD.

Conclusion

RBD is an "experiment of nature" in which knowledge from the study of motor-behavioral dyscontrol during REM sleep, with dream enactment, has cast a broad and powerful light on a multitude of CNS disturbances, their evolution, and their comorbidities. RBD has also cast light on the pervasive phenomenon of state dissociation [9, 30–33], as discussed in Chap. 28. The expanding and deepening knowledge on RBD is well reflected in the 45 chapters contained in this book.

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The Human Dimension of RBD

2

Carlos H. Schenck

"In all of us, even in good men,
there is a lawless, wild-beast nature
which peers out in sleep."

(Plato, The Republic)

The human dimension of RBD encompasses the experience of RBD in the patient and in the spouse affected by the RBD, and the adverse physical, psychological, marital, and quality-of-life consequences from the RBD, including both idiopathic RBD (iRBD) and RBD associated with Parkinson's disease (PD) and other neurological disorders.

2.1 The Experience of RBD in the Patient and Spouse

The typical clinical profile of chronic RBD consists of a middle-aged or older man with aggressive dream-enacting behaviors that cause repeated injury to himself and/or his wife. This profile was revealed in the first two large published series on RBD, involving 96 and 93 patients, respectively [1, 2]. In these two series, male predominance was 87.5 and 87%, mean age at RBD onset was 52 years and 61 years, dream-enacting behaviors were reported in 87 and 93% of patients, and sleep-related injury as the chief complaint was reported in 79 and 97% of patients. Injuries included ecchymoses, subdural hematomas, lacerations (arteries, nerves, tendons), fractures (including high cervical—C2), dislocations, abrasions/rug burns, tooth chipping,

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and hair pulling. RBD causing subdural hematomas has subsequently been reported in five additional cases [3–6]. A review of the published cases of RBD that were associated with potentially lethal behaviors identified choking/headlock in 22–24 patients, diving from bed in 10 patients, defenestration/near-defenestration in 7 patients, and punching a pregnant bed partner in 2 patients [7].

In the review just cited, the concept of "victim vulnerability factors" for increasing the risk of morbidity and mortality from vigorous RBD behaviors was discussed at length [7]. A "spectrum of vulnerability" can be formulated for RBD (and other parasomnias) whereby at one end of the spectrum is the degree of vigor and violence of the RBD behavior and at the other end of the spectrum is the degree of medical vulnerability of the victim (patient or spouse). Also, the fact that the patient or bed partner is asleep, and in which sleep stage (e.g., REM sleep with generalized muscle paralysis [REM atonia] in the bed partner or slow-wave NREM sleep in the bed partner predisposing to an agitated and violent confusional arousal induced by a RBD episode), or if the bed partner suffers from a sleep disorder predisposing to abnormal and potentially violent arousals (e.g., sleep apnea, sleep inertia, confusional arousals, sleep terrors, sleepwalking) would add an additional sleep-related vulnerability risk factor. The circumstances of the sleeping environment may also confer additional vulnerability. Some of the medical factors that can increase the morbidity and mortality risk from RBD behaviors include pregnancy, deafness, blindness, osteopenia, osteoporosis, bleeding disorder, anticoagulant therapy, status postsurgical procedure, spinal-vertebral disorder, and various advanced age-related vulnerabilities.

The experiences of the initial series of RBD patients and their spouses presenting to the Minnesota Regional Sleep Disorders Center beginning in 1982 were captured by audiotaped interviews (with signed permissions) that were transcribed and edited and then published in a book [8]. A powerful language was expressed when these patients and their spouses shared their amazing and harrowing "bedtime stories." The strength and resilience of a successful, long-term marriage reveals how "true love can shine through the darkest of nights". Usually patients with RBD have been married for decades before the onset of RBD, so the spouses know that the later-life onset of sleep violence is not reflective of the well-established waking personality. This is probably the main reason for having only two published cases of divorce and one case of marital discord related to RBD. Moreover, despite the risk of injury, the spouses (predominantly wives) often choose to sleep in the same bed, in order to protect the person (viz. husband) with RBD from becoming injured. On the other hand, RBD also carries a high risk for false accusations of spousal abuse, as described below.

A wide variety of self-protection measures have been used during sleep in RBD, including sleeping in a padded waterbed; putting the mattress on the floor; using pillow barricades; tethering oneself to the bed with dog leashes, belts, and ropes; etc. Also, misattributions about the cause of RBD are common among patients, family, friends, and physicians, including job-related stress in which the RBD would presumably resolve with retirement (not true, and often RBD progresses in severity after retirement), nocturnal psychosis, "familial alcoholic personality disorder"

coming out in sleep, dietary indiscretion, post-traumatic stress from combat exposure in World War II, or just "part of getting old, it's one of those things that happens to older people."

Melvin Abel was the second RBD patient in our initial series, and he made frequent media appearances, because of his likeability (along with his wife Harriet)—and because of his striking deer dream that was reported in *Stern* magazine (Germany), "Medicine: Hunting Deer Under the Blanket" (translation), March 24, 1988, and in *The New York Times* Sunday magazine cover story, by Chip Brown: "The Man Who Mistook His Wife For a Deer (And Other Tales From the New Science of Extreme Sleep)," February 2, 2003. What follows is the interview I had with Mel and Harriet on page 68 of *Paradox Lost* [8]:

> Harriet: "You know, we would be sitting and talking to friends, and we would tell them what he dreamed the night before, and they would sit and laugh about it. Nobody knew how serious it was."
>
> Mel: "My deer episode. When I was a little kid, I lived on a farm with my grandparents. My grandpa and me were in the haymound pitching hay around. This was my dream: I saw two deer go by the haymound and I told my grandpa, 'Did you see those deer?' He said, 'No, where did they go?' I said, 'They must have gone to the other end of the barn.' He says, 'I'll go down and roust them out,' and I said, 'I'll wait here with the pitchfork and maybe I can get the doe.' All of a sudden, here came that doe and I bashed her as hard as I could across the neck and down she went and laid there and blatted. 'I know how to fix that up; just get you by the chin and head, and snap your neck.' I reached over—and I got Harriet by the chin, and I just put my hand on top of her head, and she let out a holler, and jumped out of bed and said, 'What in the world are you trying to do?' I then came-to and I sat there for a while and then I started to cry."
>
> Harriet: "He was afraid of hurting me and what could have happened. He was upset."
>
> Mel: "I told her, 'God, am I glad that you woke me up.' She says, 'what were you trying to do?' I said, 'I was going to break that deer's neck. Just think what would have happened if you wouldn't have hollered.'"
>
> Harriet: "Many times he would swing his arm and I thought I may get a black eye or broken nose. How am I going to say, 'Look what happened to me while my husband was sleeping.' Nobody would believe me."

Additional dialogues, and comments on the imminent dangers posed by RBD, are contained in Tables 2.1 and 2.2.

There have been two reported cases of divorce related to RBD [9, 10]. The first case involved a 28-year-old Italian man with narcolepsy type 1 for 8 years, and subsequent RBD, who 3 years earlier had married an 18-year-old female [9]. His young wife reported that from almost the start of their marriage, he screamed and episodically hurt her during sleep by kicking and slapping her. After 2 years of marriage, one night at 4 a.m. while she was asleep, he violently punched her, and then he lay down again and resumed sleep. She went to another room and locked the door. The next morning she went to the hospital because of intense breast pain, and an ultrasound revealed a 4 cm^3 hematoma. The police were notified by the doctor, but she refused to press charges. The husband was "astonished and mortified" and reported that he only recalled that he "attempted to escape during a dream." After he punched her again (in the face) while asleep, they agreed to sleep in separate rooms.

Table 2.1 Sample dialogues of men with RBD and their wives[a]

A 57-year-old man with RBD and wife
• "It seems like I am extra strong when I sleep"—man
• "It almost seems like a force picks him up"—wife
• "He is sleeping and his body is in motion"—wife
• "I don't think he ever could hit as hard while awake as he hits during sleep. A year ago he punched right through a wall board in our bedroom at our lake cabin"—wife
• "Oh yes, there were always bloody sheets" wife
A 67-year-old man with RBD and wife
• "It's amazing. You should see the energy behind that activity. Oh, it's so unreal."—wife
• "He pounded my head one night and my head still hurt for another 2 weeks."—wife
• "His legs go fast, just like he's running."—wife
• "We've put as much distance between us in bed as we can."—wife
• "I didn't really sleep soundly until he got up in the morning."—wife
A 65-year-old man with RBD and wife
• "I was wrestling someone and I had her by the head. What scares me is what a catastrophe that would be to wake up and find that I had broken her by the neck."—man
• "This went on for 3 years, and then I retired—but nothing changed afterwards whatsoever."—man
• "What happens to people like my husband who don't get diagnosed? Do they kill their wives in these experiences? Do we know?"—wife
A 70-year-old man with RBD and wife
• "I didn't remember the dream because I knocked myself out"—man
• "The next morning I asked her what I had done, and she told me I had beat her"—man
• "It was hard for me to sleep, because I never knew when I was going to get hit"—wife
• "When all this started, I figured it was part of getting old, part of being normal, I guess"—wife
A 75-year-old man with RBD and wife
• "I just started kicking—the big, faceless, shapeless figures were still there. And my wife was afraid for herself, the dog, and for me"—man
• "I told him I'd have a Devil of a time explaining how I got a broken arm in bed with both of us asleep"—wife
• "When a man his size comes down on that floor, honestly, it's a miracle he has not broken a hip or a shoulder"—wife

[a]From reference [8]

Table 2.2 Comments by patients and spouses on RBD behaviors causing imminent danger[a]

1. *Comments by RBD patients*
"I ran right smack into the wall, an animal was chasing me. I think it was a big black dog" (p. 157)
"I thought I was wrestling someone and I had her by the head" (p. 136)
"Pounding through the curlers into her head" (p. 157)
"What scares me is what a catastrophe that would be to wake up and find that I had broken her neck" (p. 137)
"I have hit her in the back too, and she has had a couple of (vertebral) disc operations." (p. 143)

(continued)

Table 2.2 (continued)

"One night I woke up as I was beating the hell out of her pillow…that's when I realized that I had a problem" (p. 106)
"Just recently, I rammed into her pelvis with my head…during a dream." (p. 93)
2. *Comments by the wives*
"It's amazing. You should see the energy behind that activity, oh, it's unreal."(p. 107)
"He literally just kind of flew out of bed and landed on the floor with tremendous strength" (p. 53)
"It almost seems like a force picks him up." (p. 130)
"His legs go so fast, just like he's running" (p. 155)
"It is his kicking, violent kicking, his feet are just like giant hammers when they hit you over and over again" (p. 73)
"I felt that kick on the ankle for two months afterwards" (p. 82)
"That's the reason we got the waterbed—because he was wrecking his hands on the wooden bed" (p. 111)
"Oh, yes, there were always bloody sheets" (p. 105)
"Roaring like a wounded wild animal: he roared, he crouched, he punched" (p. 75)

[a]From reference [8]

Seven months later he underwent a full sleep evaluation that confirmed the diagnoses of narcolepsy type 1 and RBD. However, the wife was not fully convinced of the husband's unintentional nocturnal violence, and 6 months later she left him and reported the nocturnal beatings. At trial, he was fully acquitted because the violence toward the wife was determined to have originated from sleep (i.e., RBD).

The second case of RBD causing divorce involved a 63-year-old Chinese man whose four consecutive wives had divorced him because of his aggressive and violent dream-enacting behaviors, including repeated biting [10]. For example, with his first wife, one night he dreamed that he was eating an apple, but instead he was biting her ear. On subsequent nights, during similar dreams he would bite her ears, nose, and face, which culminated with his wife divorcing him after 4 years of marriage. His three next marriages were also terminated by the wives on account of his repeated RBD-related sleep violence, including aggressive biting during dreams. These marriages had lasted 2.5 years, 10 years, and 1.5 years, respectively. In addition, three brief relationships with girlfriends were also terminated for the same RBD-related reasons. After the eventual diagnosis of RBD by clinical sleep evaluation and vPSG, therapy with clonazepam, 0.5 mg at bedtime, was successful in substantially controlling the RBD.

Another case of RBD with biting involved duloxetine-induced RBD in a 62-year-old woman who one night dreamed of biting something, but she was actually biting the hand of her grandson [11]. Also, in a series of 203 consecutive idiopathic RBD patients, the prevalence of biting in RBD was 8.4%, which usually involved bed partners [12]. The full range of personal consequences from the RBD in these 203 patients and their spouses is described in detail in Chap. 4 by Alex Iranzo, one of the authors of that study.

There was an additional published case of marital discord, without divorce, caused by RBD [13]. A recently married, young adult Taiwanese woman with RBD attempted suicide because her husband would not sleep with her at night after complaining that her RBD disrupted his sleep excessively and compromised his work productivity. Fortunately, once her RBD was diagnosed and effectively treated with clonazepam, the husband resumed sleeping with her (albeit in a larger bed), and their marriage was preserved.

Violent RBD carries an increased forensic risk, including both inadvertent death ("parasomnia pseudo-suicide" [14]) and inadvertent homicide [15]. The manifestations and associated issues related to milder forms of RBD are discussed in Chaps. 11, 15, and 16.

2.2 Other Issues Related to the Personal Experience of RBD

Although RBD usually features dream enactment of fighting with unfamiliar people or animals, a series of five patients with atypical dream-enacting behaviors in RBD has been reported, involving abuse/retaliation dreams, a culture-specific dream, and a religion-specific dream [16]. A 43-year-old female had repeated dream enactment observed by her husband in which there were defensive posturing, arm flailing, and punching that corresponded to dreams of her mother and sister who often berated her and beat her during childhood. She never retaliated in childhood, but only later during dream enactment with RBD. Clonazepam controlled RBD dream-enacting behaviors and the associated retaliation dreams. A 43-year-old man developed RBD with "fighting dreams" observed by his wife that involved hitting back at his previously verbally and physically abusive alcoholic father. A 58-year-old married man developed RBD with some of his recurrent dream enactments involving "punching out" a hypercritical father during his childhood, while he was actually hitting his wife in bed. In the mornings upon awakening, he never felt remorse about his retaliation dreams against his father, but felt remorse over hitting his wife while asleep. Prior to developing RBD, he did not have retaliation dreams, but did have dreams about his hypercritical father. Clonazepam therapy at bedtime controlled both the dream-enacting behaviors and the retaliation dreams. An example of culture-specific dream enactment involved a 51-year-old Japanese man who enacted a classic Samurai warrior film sequence during a presumed RBD episode captured by a home sleep video recording (prior to vPSG confirmation of his RBD). The episode lasted from 2:43:58 a.m. to 2:45:59 a.m. and culminated with his grabbing an imaginary sword with both hands and stabbing vigorously up and down 12 times in rapid succession. A religion-specific dream enactment involved a 26-year-old Taiwanese man with narcolepsy type 1 and RBD. He was a devote Taoist, and three times daily at home he enacted a Taoist temple worship ceremony with prayer that lasted almost 5 min. During a vPSG study, in REM sleep he faithfully enacted this temple worship ceremony in the sleep lab bed, with sitting up, kneeling and fully bowing down, immobile, but with full muscle tone, while softly chanting his prayer.

Knowledge about the range of behaviors and associated clinical features in RBD continues to expand. For example, one study searched for laughing during RBD

episodes [17]. Records of 67 consecutive vPSG recordings of RBD patients at a neurological sleep center were reviewed and found that 21% (14/67) had repeatedly laughed during REM sleep, with 71% (10/14) being males and with a mean age of 63 ± 11 years. Ten of these 14 patients had idiopathic PD, 3 had multiple system atrophy, and 1 patient had dementia with Lewy bodies. Other RBD-associated behaviors included smiling, crying, aggression, screaming, and somniloquy. Therefore, laughing was documented to belong to the spectrum of behavioral manifestations of RBD. A notable finding was that 9/14 patients (64%) with laughing during RBD episodes were clinically depressed during daytime, thus indicating a state-dependent dissociation between waking vs. REM sleep emotional expression in RBD, at least in the context of an alpha-synuclein neurodegenerative disorder.

A surprising feature of RBD dream enactment is how sexual dream content and sexual acting-out behavior are virtually never reported. Freud would have been surprised, as the loss of REM atonia and the emergence of RBD would appear to be an ideal context for sexual acting-out. However, there is a shift in the bias of dream content with RBD, away from sex and toward confrontation and fighting [18]. On the other hand, "sexsomnia" (i.e., sexual behaviors during sleep) is a well-documented parasomnia that typically emerges from deep NREM sleep and that involves the release of a full spectrum of sexual behaviors without associated dreaming [19]. So "sexual acting-out" in sleep is not linked with dreaming, a distinctly non-Freudian phenomenon.

2.3 Adverse Consequences from RBD and Quality-of-Life Issues

RBD is associated with major quality-of-life (QOL) burdens. Repeated injuries to self and spouse are common, including potentially lethal behaviors [1, 2, 7, 12]. There are also marital burdens [9, 10, 12, 13, 20, 21] and worse motor and nonmotor symptoms and QOL in RBD-PD compared to PD-without RBD [22–24].

A cross-sectional study in idiopathic RBD (iRBD) was recently reported on the impact of "noxious" RBD symptoms (most notably recurrent sleep-related injuries) on the spouses affecting the quality of their sleep and their physical, mental, and marital well-being [20]. Results were compared to those from spouses of age- and sex-matched obstructive sleep apnea (OSA) patients. Forty iRBD patients (90% male) and their spouses and 35 OSA patients (80% male) and their spouses were studied. Almost all iRBD spouses (90%) reported disturbances from the nocturnal RBD behaviors of their bed partners; 62.5% of the iRBD spouses reported a history of being injured during sleep. Spouses of both iRBD and OSA patients reported a comparably high prevalence of insomnia, anxiety, and depressive symptoms. Spouses of iRBD patients, however, reported more impaired quality of life and adverse effects on the marital relationship from the RBD behaviors. However, nearly two-thirds of RBD couples continued co-sleeping, despite the ongoing risk of sleep-related injuries and secondary nocturnal sleep disturbances affecting the spouse (as described in the previous section of this chapter). The authors concluded that both iRBD and OSA spouses exhibited a high prevalence of insomnia and mood problems. In particular,

iRBD significantly and negatively affect the spouses' quality of life and the marital relationship.

In another study, QOL was negatively impacted in patients with probable RBD (pRBD) (questionnaire based) and early PD, compared to early PD patients without pRBD in a study of 475 PD patients evaluated within 3.5 years of PD diagnosis [22]. There was a 47% frequency of pRBD (without any prior recognition). The two groups did not differ on motor phenotype, and they scored comparably on objective motor scales. However, the pRBD group more frequently reported problems with the motor aspects of daily living, and also the pRBD group had significantly greater cognitive impairment, sleepiness, and depression. This study calls attention to how pRBD (and presumably vPSG-confirmed RBD) is both common and under-recognized in patients with early PD. Furthermore, pRBD is associated with both increased severity and frequency of non-motor features of PD, with diminished motor performance, and a greater negative impact on health-related quality of life.

A case-control study from Japan evaluated the characteristics of nocturnal disturbances and other motor and non-motor features related to RBD in patients with PD and the impact of RBD on their quality of life [23]. A consecutive series of 93 PD patients was gathered, with mean age of 70 years, involving 50 men and 43 women, along with 93 age- and gender-matched control subjects. The mean disease duration in the PD patients was 6.8 ± 6.1 years. pRBD was evaluated using the Japanese version of the RBD screening questionnaire (RBDSQ-J). When comparing PD patients with pRBD (n = 18) and those without pRBD (n = 59), after the exclusion of RLS and snorers, the pRBD group showed a higher rate of early morning dystonia and higher scores of UPDRS IV and PDSS-2 total scores than the non-pRBD group. The Parkinson's Disease Questionnaire (PDQ-39) domain scores for cognition and emotional well-being were higher in the patients with pRBD-PD compared to PD patients without pRBD. The pRBD group showed higher scores compared with the non-pRBD group on the Parkinson's disease sleep scale-2 (PDSS-2) total and subscores (insomnia, distressing dreams) and distressing hallucinations. There were no differences between these two groups with respect to the clinical subtype, disease severity, or motor function.

Another study aimed at understanding the impact of having RBD on multiple non-motor symptoms (NMS) in patients with PD [24]. Eighty-six PD patients were clinically and vPSG evaluated for RBD and assessed for multiple NMS of PD. Seven NMS measures were assessed: cognition, quality of life, fatigue, sleepiness, overall sleep, mood, and overall NMS of PD. RBD was a significant predictor of increased NMS in PD while controlling for dopaminergic therapy and age. The RBD group reported more NMS of depression, fatigue, and overall NMS.

Therefore, there is converging evidence that RBD is a marker of widespread neurodegeneration in PD, with PD-RBD patients vs. PD-without-RBD patients being more severely impaired across motor and non-motor domains, as discussed in Chaps. 5 and 35. The increased levels of PD motor impairment also include axial symptoms, such as postural instability with falls, freezing of gait, and dysarthria. There are increased levels of cognitive impairment (with increased risk for

dementia), visual hallucinations, autonomic dysfunction, and greater impairment in quality-of-life status.

Finally, a study was recently published on quality of life in Korean idiopathic RBD patients [25]. Sixty patients (mean age, 61 years; 36 males, 24 females) had PSG-confirmed RBD and completed a MMSE and the Short-Form 36-Item Health Survey for quality of life. Idiopathic RBD patients were compared with patients with restless legs syndrome, type 2 diabetes mellitus, hypertension, and healthy controls. The total quality-of-life score in idiopathic RBD was significantly lower than that for healthy controls but higher than in the other patient groups. Nevertheless, idiopathic RBD was found to have a significant negative impact on quality of life.

Note Added in Proof: A recent case of antidepressant-induced RBD with major injuries has been published [26]. And in regards to biting during RBD episodes described in section 2.1 and in references [10–12], the differential diagnosis of sleep-related biting has recently been published [27].

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The Foundation of the International RBD Study Group (IRBDSG)

3

Wolfgang Oertel, Geert Mayer, Aaro V. Salminen, and Carlos H. Schenck

3.1 Introduction

The International RBD Study Group (IRBDSG) was founded on September 29, 2009, in Monte Verità, Ascona, Switzerland, during the 6th International Symposium on Narcolepsy. So the setting of an international conference on a major REM sleep disorder, viz., narcolepsy, was also the setting for the founding of an international research group focused on another major REM sleep disorder, viz., RBD. A small, dedicated group of scientists and clinicians with a common vision and sense of purpose came together to form the IRBDSG (Table 3.1).

It should also be recognized that the IRBDSG was primarily the brainchild of one of the authors (WO, as hereby acknowledged by the other authors). Wolfgang Oertel spearheaded the early formation of the IRBDSG in 2007 and 2008 by being the primary organizer of these highly stimulating RBD research symposia* (to be further discussed in Sect. 3.4 below):

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https://doi.org/10.1007/978-3-319-90152-7_3

Table 3.1 Founding members of the IRBDSG in 2009

Last name	First name	Title	Affiliation
Dauvilliers	Yves	Prof.	Department of Neurology, Hôpital Gui de Chauliac, Montpellier, France
Ferini-Strambi	Luigi	Prof.	Sleep Disorders Center, Università Vita-Salute San Raffaele, Milan, Italy
Gaig	Carles	Dr.	Hospital Clinic de Barcelona, Barcelona, Spain
Högl	Birgit	Prof.	Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
Jennum	Poul	Prof.	Department of Clinical Neurophysiology, University of Copenhagen, Copenhagen, Denmark
Iranzo	Alexander	Dr.	Neurology Service, Hospital Clinic de Barcelona, IDIBAPS CIBERNED, Barcelona, Spain
Luppi	Pierre-Hervé	Prof.	University of Lyon and Lyon Neuroscience Research Center, Lyon, France
Mayer	Geert	Prof.	Hephata Clinic, Treysa and Department of Neurology, Philipps University Marburg, Germany
Möller	Jens Carsten	PD Dr.	Department of Neurology, Philipps University, Marburg, Germany
Montplaisir	Jaques	Prof.	Hôpital du Sacré-Coeur de Montréal, Department of Psychiatry and Neurosciences, University of Montreal, Quebec, Canada
Overeem	Sebastiaan	Dr.	Medical Center, Radboud University, Nijmegen, The Netherlands
Oertel	Wolfgang	Prof.	Department of Neurology, Philipps University, Marburg, Germany
Partinen	Markku	Prof.	Skogby Sleep Clinic, Espoo, Finland
Plazzi	Giuseppe	Dr.	Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
Schenck	Carlos H.	Dr.	Minnesota Regional Sleep Disorders Center, Department of Psychiatry, Hennepin County Medical Center, and University of Minnesota Medical School, Minneapolis, MN, USA
Sonka	Karel	Dr.	Department of Neurology, Charles University and General University Hospital, Prague, Czech Republic
Urade	Yoshihiro	Prof.	Osaka Bioscience Institute, Osaka, Japan

*1st International Marburg Symposium on REM Sleep Behavior Disorder (Sleep Disorders Meet Movement Disorders), Philipps-Universität, Marburg, Germany, September 21–23, 2007.

2nd International Marburg Symposium on REM Sleep Behavior Disorder (From Early Diagnosis to Therapeutic Intervention–Sleep Medicine Meets Neurodegeneration), Philipps-Universität, Marburg, Germany, October 18–20, 2008, sponsored in part by the Movement Disorder Society, European Section.

3.2 What Were the Reasons and Guiding Ideas that Started This Group?

There were at least four reasons:

2.1: In 1996, Schenck, Bundlie, and Mahowald published their landmark article on REM sleep behavior disorder as a potential prodromal stage of Parkinson's disease (PD) and related syndromes [1]. When the follow-up data by the same group were presented in an abstract form with its—at least for that time—surprisingly high conversion rate (65%) of RBD into the alpha-synucleinopathies (see 2.2), viz., PD, dementia with Lewy bodies (DLB), and rarely multiple system atrophy (MSA) [2], the scientific community started to realize the impact of this RBD finding for research on prodromal stages of neurodegenerative disorders.

2.2: The discovery of the A53T mutation in the gene for alpha-synuclein as the cause for the (although very rare) autosomal-dominant form of Parkinson's disease [3], the subsequent demonstration of alpha-synuclein aggregates in the Lewy bodies of the postmortem substantia nigra of PD patients [4], and the publication of the Braak staging [5] led to a scientific revolution in the research field on prodromal and manifest PD.

2.3: Based on 2.1 and 2.2 inside the sleep research community, the idea of creating an International RBD Study Group was discussed during the 2nd WASM (World Association of Sleep Medicine) Congress in Bangkok in February 2007 and by a "RBD Task Force" at the meeting of the American Academy of Sleep Medicine (AASM) in Seattle 2007. In these meetings scientists and clinicians were discussing standards and the preparation of a consensus article on scoring REM sleep without atonia (RSWA).

2.4: Inspired by the articles of Schenck and coworkers [1, 2, 6] and coming from the field of movement disorders, the research group on PD at the Department of Neurology, University of Marburg, Germany (WO), together with the sleep disorder research group at the Hephata-Klinik in Treysa near Marburg, Germany (GM), published an article which for the first time provided evidence that patients with RBD in fact presented Braak stage 1, i.e., hyposmia; Braak stage 2, i.e., RBD, related to a lesion of the REM sleep control centers in the brain stem; and Braak stage 3, i.e., a subclinical degeneration of the nigrostriatal tract as demonstrated by FP-CIT SPECT—in the same individual—in accordance to the Braak staging of prodromal PD [7]. Looking together at the events described under 2.1, 2.2, and 2.3, it became obvious that the "dream-sleep disorder" RBD, previously considered to be a "rare disease," would most likely play a key role in the search for a neuroprotective or neuropreventive therapy for PD, DLB, and/or MSA. At that time the group in Marburg had programmed an electronic Internet-based data system for standardized clinical documentation of RBD patients. Having a functioning tool to offer to RBD specialists, it was decided in 2005 to invite RBD groups from all over the world for a first meeting in Marburg to create an international RBD network.

3.3 The State of the RBD Research Field Around 2006

Twenty years after its first description by C. Schenck and coworkers [6], the peer-reviewed medical literature on RBD in 2006 was just starting to increase (Fig. 3.1).

Being a rather recently discovered disorder, it was a challenge to study its symptoms, etiology, and pathophysiology and—at least as important—to create diagnostic standards. At that time the only known treatment was a benzodiazepine (clonazepam), although this therapeutic recommendation was based on open-label case series. Therefore, one of the most urgent needs was to establish the basis for studies with established and new drugs. The patient cohorts presented in publications were rather small and not sufficient to allow prospective randomized, placebo-controlled, double-blind studies with new substances that could provide Class I evidence-based medicine for symptomatic therapy. The goal to eventually study compounds with potentially disease-modifying effects on the prodromal progression of PD, however, required a commitment to engage in methodological efforts to define biomarkers which would allow investigators to measure progression of this prodromal stage of PD and to allow predicting the time to conversion from prodromal to manifest PD. To solve all these issues, larger patients groups were needed requiring collaboration of several centers with expertise in sleep disorders and movement disorders. So the need to create an International RBD Study Group was obvious.

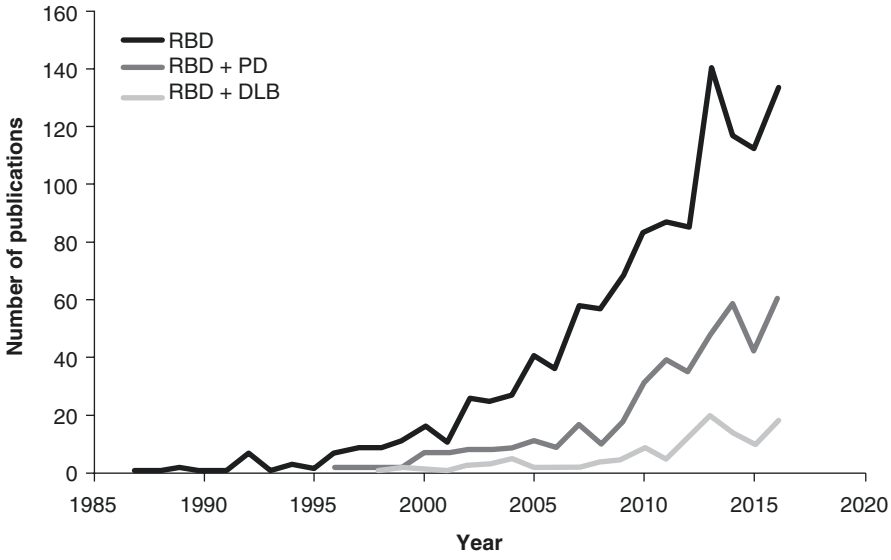

Fig. 3.1 The number of publications is visualized by year. All publications on RBD (black) can be compared to the publications mentioning in the title both RBD and Parkinson's disease (dark gray) or the publications mentioning in the title both RBD and dementia with Lewy bodies (light gray) published in each year. The data was generated using PubMed search

3.4 The Start of the International Symposia Series on REM Sleep Behavior Disorder

In 2005 the Department of Neurology, Marburg, Germany, had more than a decade-long experience with implementing large national and international consortia related to PD, restless legs syndrome, or narcolepsy. For these consortia respective Internet-based databases for standardized clinical documentation had been programmed and were freely available. Considering the future impact of RBD for the field of PD, we decided to propose the creation of an international RBD study consortium. Therefore contacts were made to international RBD sleep experts who also had expressed a similar intention. These experts accordingly promoted this idea at the conferences of the WASM and AASM in 2007 (see 2.3). A preliminary consensus was reached in January 2007 with the group in Marburg to organize an international RBD symposium with the aim to discuss the idea of an International RBD Study Group in person. This first meeting with the title "Sleep Disorders Meet Movement Disorders" was organized in September 2007 by Wolfgang Oertel, Carsten Möller, and Geert Mayer in Marburg, Germany. About 30 basic scientists and physician scientists of different RBD research groups were invited, and nearly everybody agreed to attend. The program of this first meeting (Table 3.2) and topics discussed (Table 3.3) are summarized. At this meeting the idea of a common databank—based on the existing RBD database—was presented.

Table 3.2 Program of the first International Symposium on RBD, Marburg, 2007 titled "Sleep Disorders Meet Movement Disorders"

Welcome and introduction	Wolfgang Oertel, Marburg, Germany
Session 1—Chair	Bradley Boeve, Rochester, USA
Sleep disorders in Parkinson's disease	Joan Santamaria, Barcelona, Spain, Claudia Trenkwalder, Kassel, Germany
Epidemiology and clinical markers of RBD	Karin Stiasny-Kolster, Marburg, Germany
The flip-flop switch in RBD	Jun Lu, Boston, USA
Circuits regulating muscle tone across the sleep-wake cycle	Jerome Siegel/Y. Lai, Los Angeles, USA
Physiological and anatomical links between parkinsonian syndromes and clinical and subclinical RBD	Carlos Schenck, Minneapolis, USA
Session 2—Chair	Jaques Montplaisir, Montreal, Canada
Neuropathology of preclinical and early PD	Heiko Braak, Frankfurt, delivered by Carsten Möller, Marburg, Germany
Current polysomnographic criteria for diagnosing RBD	Geert Mayer, Marburg-Treysa, Germany
Neuropsychology in RBD	Luigi Ferini-Strambi, Milano, Italy
New proposals for the diagnosis of RBD	Marco Zucconi, Milano, Italy
Session 3—Chair	Geert Mayer, Marburg, Germany
Longitudinal studies of patients with RBD	Jacques Montplaisir/Ron Postuma, Montreal, Canada

(continued)

Table 3.2 (continued)

Comorbidity of RBD	Pasquale Montagna/Giuseppe Plazzi, Bologna, Italy
Neuroimaging in RBD and alpha-synucleinopathies	Susanne Knake/Marcus Unger, Marburg, Germany
Present therapeutic options in RBD	Birgit Högl, Innsbruck, Austria
Future therapeutic issues	Wolfgang Oertel, Marburg, Germany
Session 4—Chair	Wolfgang Oertel, Marburg, Germany
Final discussion and consensus statement	All participants

Table 3.3 Topics discussed at the first International Symposium on RBD

Topic 1: What do we need?	Topic 2: A potential result of this meeting? Which type of study you cannot perform alone?	Topic 3: What do we study?
Animal models of RBD	Standardize diagnosis of RBD	Ontogenesis of REM sleep
Look for RBD in existing animal models	Standardize clinical testing	Phylogenesis of REM sleep
Genetics of RBD	Standardize clinical documentation	REM sleep in children
Diagnosis of RBD	Internet-based database with sophisticated rights for sharing data	Physiological role of REM sleep
Therapy of RBD	Collection of DNA for phenotype/genotype research	Animal models of RBD
Cohorts of RBD patients with long-term follow-up	Standardize acquiring and storing of bioprobes: blood, DNA, RNA, CSF, skin biopsy for fibroblasts, others	Genetics of RBD
Improve designs for neuroprotection trials in patients with RBD	Design of therapeutic trials – Symptomatic trials – Neuroprotective trials	Pathophysiology of RBD
Search for biomarker to be used as primary endpoint in clinical protection trials	Define and improve outcome parameters for therapeutic trials	Diagnosis of RBD Therapy of RBD

This meeting was followed by the second meeting in September 2008 – again in Marburg. At these two symposia, it became obvious that a legal body with an official structure would be helpful to realize the ambitious goals of the group (see Table 3.3, see Chap. 5, bylaws).

3.5 The Foundation of the International RBD Study Group and Its Officers from 2009 to 2017

For founding the International RBD Study Group (IRGDSG), we took the opportunity to meet at the 6th International Symposium on Narcolepsy in Ascona, Switzerland, organized by Claudio Bassetti, Christian Baumann, and Thomas Scammell. For at this occasion, basic scientists and physician scientists from

Table 3.4 The list of the officers of the IRBDSG from 2009 to 2017

Position	2009–2011	2011–2013	2013–2015	2015–2017
President	C. Schenck	J. Montplaisir	W. Oertel	I. Arnulf
President elect	J. Montplaisir	W. Oertel	I. Arnulf	B. Boeve
Past President	–	C. Schenck	J. Montplaisir	W. Oertel
Secretary	L. Ferini-Strambi	A. Iranzo	B. Högl	A. Videnovic
Secretary elect	A. Iranzo	I. Arnulf	A. Videnovic	Y.E. Ju
Treasurer	P.H. Luppi	G. Mayer	Y. Inoue	Y.K. Wing
Treasurer elect	G. Mayer	Y. Inoue	Y.K. Wing	A. Heidbreder

various areas of sleep medicine and neurodegeneration were present. The meeting took place on September 29, 2009, in Monte Verità overlooking Ascona. The first board was elected by the assembly of the founding members with terms of 2 years. The list of the officers of the IRBDSG from 2009 to 2017 is found in Table 3.4.

At the meeting in Monte Verità, Ascona, in 2009, a first draft of the bylaws was presented. The final bylaws were discussed and approved in the constitutional meeting in Montreal, Canada, in 2010.

The bylaws state the aims of the IRBDSG as follows:

Objective of the association is the promotion of the international scientific research in the field of REM sleep behavior disorder and associated fields and the optimization of medical care for patients by improving diagnostic and therapeutic measures. A close co-operation of physicians, scientists, as well as patients and their family members is to be developed further and will facilitate a fast knowledge and information exchange in the field of REM sleep behavior disorder and associated fields. Therefore the association wants to contribute to and improve the international information and communication structures and to support the establishment of standardized patient data bases.

The statute's purpose in particular will be carried out by the following measures

- *fusion and integration of international experts within the field of REM sleep behavior disorder and associated fields*
- *initiation and execution of scientific projects in basic and clinical research as well as research in health care of REM sleep behavior disorder and associated fields which are not or only partly supported by public organizations or industrial sponsoring*
- *execution of scientific meetings, seminars and advanced training activities*
- *co-operation with other scientists and scientific organizations, research projects or consortia, that could support the objectives of the association in the field of REM sleep behavior disorder, associated fields and related fields*
- *assignment of research contracts to universities or non-profit organizations*
- *publication of research results, guidelines, and recommendations for socio-legal aspects and unmet needs*
- *transfer of results into applicable tools*
- *cooperation and support by public organizations, self-help groups and industry*
- *to provide grants to members and non-members for participation in scientific and educational meetings.*

The approved finalized bylaws were submitted to the Charity Registry in Marburg, Germany, and were accepted. The members chose not to raise a membership fee. This decision was changed at the meeting in Ravenna 2016.

3.6 Consensus Criteria Workshop 2010

At the fourth meeting of the IRBDSG in 2010 in Marburg, a state-of-the-art article [8] was drafted and subsequently published in 2013 (Table 3.5).

Table 3.5 Authors and centers participating in the consensus criteria article published in 2013 (Schenck CH, Montplaisir JY, Frautscher B, Hogl B, Gagnon JF, Postuma R, Sonka K, Jennum P, Partinen M, Arnulf I, Cochen de Cock V, Dauvilliers Y, Luppi PH, Heidbreder A, Mayer G, Sixel-Döring F, Trenkwalder C, Unger M, Young P, Wing YK, Ferini-Strambi L, Ferri R, Plazzi G, Zucconi M, Inoue Y, Iranzo A, Santamaria J, Bassetti C, Moeller JC, Boeve BF, Lai YY, Pavlova M, Saper C, Schmidt P, Siegel JM, Singer C, St Louis E, Videnovic A, Oertel W, 2013 *Sleep Medicine*) [8]

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• Department of Neurology, McGill University, Montreal General Hospital, Quebec, Canada
• Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic
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• Helsinki Sleep Clinic, Vitalmed Research Centre, Helsinki, Finland
• Unite des pathologies du sommeil, Hôpital Pitié-Salpêtriére, APHP and INSERM U975-CRICM-Pierre and Marie Curie University, Paris, France
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• Department of Biomedical and NeuroMotor Sciences, University of Bologna and IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
• Neuropsychiatric Research Institute, Japan Somnology Center, Tokyo, Japan
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• Department of Neurology Inselspital, University Hospital Bern, Bern, Switzerland
• Neurocenter of Southern Switzerland, Ospedale Regionale Civico Lugano, Lugano, Switzerland

(continued)

Table 3.5 (continued)

• Department of Neurology and Center for Sleep Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA
• UCLA Department of Psychiatry, Sepulveda VA Medical Center, Neurobiology Research, Sepulveda, CA, USA
• Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA
• Department of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA
• National Parkinson Foundation, Miami, FL, USA
• Department of Neurology, University of Miami School of Medicine, Miami, FL, USA
• Department of Neurology, Northwestern University, Chicago, IL, USA
• Department of Neurology, Philipps University Marburg, Marburg, Germany

Table 3.6 Past and planned meetings of the IRBDSG

Year	Location	Organizer	Connected to an international meeting/stand-alone meeting
2007	Marburg, Germany	Wolfgang Oertel	Stand-alone meeting
2008	Marburg, Germany	Wolfgang Oertel	Stand-alone meeting
2009	Ascona, Switzerland	Founding meeting	6th International Symposium on Narcolepsy
2010	Montréal, QC, Canada	Jaques Montplaisir	AASM
2011 (May)	Marburg, Germany	Wolfgang Oertel	Stand-alone meeting—Consensus article
2011 (Oct)	Otsu, Shiga/Kyoto, Japan	Yuichi Inoue	WFSRS
2012	Montvillargenne/Paris, France	Isabelle Arnulf	ESRS
2013	Valencia, Spain	Alexander Iranzo	WASM
2014	Gustavelund/Helsinki, Finland	Markku Partinen	ESRS
2015	Fort Lauderdale, FL, USA	Erik St. Louis/ Bradley Boeve	International Symposium on DLB
2016	Ravenna, Italy	Giuseppe Plazzi	ESRS
2017	Prague, Czech Republic	Karel Sonka	WASM/WSS
2018	Bad Kohlgrub/München, Germany	Wolfgang Oertel	Stand alone meeting–13.-16.09.2018

Abbreviations: *AASM* American Academy of Sleep Medicine, *ESRS* European Sleep Research Society, *WASM* World Association of Sleep Medicine, *WFSRS* World Federation of Sleep Research Societies, *WSS* World Sleep Society

3.7 The Series of International Symposia of the IRBDSG

Following the first two meetings in 2007 and 2008 and after the foundation of the IRBDSG in 2009, annual meetings have been held, and the number of participants/members has been growing steadily (66 members from 15 countries in 2016). See also group photograph of the IRBDSG meeting in Ravenna 2016 (Table 3.6 and Fig. 3.2).

Fig. 3.2 Group photo of the participants of the IRBDSG meeting in Ravenna 16-181016. Starting in the back from left to right. *Back row:* Ron Postuma, Michel Cramer Bornemann, Aleksandar Videnovic, John Peever, Marco Zucconi, Jaques Montplaisir, Michel Silber, J-F Gagnon, Marco Terzaghi, Raphaele Ferri, Yves Dauvilliers, Karen Sonka. *Middle row:* Raffaele Manni, Pierre-Herve Luppi, Bradley Boeve, Dario Arnaldi, Erik K. St. Louis, Aureli Soria-Frisch, Luigi Ferini-Strambi, Geert Mayer, Ki-Young Jung, Alex Iranzo, Carlos Schenck, Dieter Kunz, YK Wing, Anna Fernandez-Arcos, Anna Heidbreder, Birgit Högl, Carlo Alberto Tassinari, Fabio Pizza. *Front row:* Thomas Barber, Giuseppe Plazzi, Michel Hu, Wolfgang Oertel, Markku Partinen, Poul Jennum, Friederike Sixel-Döring, Federica Provini, Stine Knudsen, Isabelle Arnulf, Yo-El Ju, Valerie Cochen de Cock, Ambra Stefani, Elena Antelmi, Nana Tachibana

3.8 Achievements of the IRBDSG

- The meetings have launched the exchange of ideas and projects among basic researchers and clinical investigators. This communication has promoted multiple national and international studies and scientific initiatives, with publication of findings in noted peer-reviewed journals, which have led to an increase of knowledge and the dissemination of the latest information about RBD and its consequences in medical teaching and multidisciplinary training. The IRBDSG has set standards that will be updated at regular intervals.

Achievements of the IRBDSG

- 11 I-RBD-SG meetings to date.
- Participation in the diagnostic classification of RBD for the International Classification of Sleep Disorders (ICSD-3) (Carlos H. Schenck represented the IRBDSG).

- Nine peer-reviewed journal publications [9–17].
- Database (Internet) programmed (193 datasets available).
- Drafts of clinical trial protocols for pharmacological interventions – written by several members of IRBDSG.
- Members in the following projects
  - Parkinson Progression Marker Initiative (PPMI) (Michael J Fox Foundation (MJFF)) – prodromal cohort RBD
  - COURAGE-PD (2014–2017) – Joint Programming Neurodegenerative Diseases (JPND, European Research Framework)

3.9 What More Needs to Be Achieved

Website of the IRBDSG
Clinical trial on symptomatic therapy
Implement counseling for patients with RBD diagnosis concerning the development of neurodegenerative disease
Motivate patients and relatives to donate for national brain banks
International biosample databank
International updated guidelines for the diagnosis and treatment of RBD
International grant support

3.10 Mission and Vision statement of the IRBDSG

In 2018 the IRBDSG defined and approved a „Mission and Vision Statement". This statement says:

IRBDSG: Diagnosis – Treatment – Pathophysiology – Neurodegenerative Disease Modulation

Mission: The IRBDSG represents a core group of clinicians and scientists who are committed to advancing knowledge in REM sleep behavior disorder, particularly: definition and diagnostic criteria, pathophysiology, clinical and polysomnographic phenomenology, and relevance to neurologic disease and neurodegeneration.

Vision: We envision a world where RBD 1) is better recognized by the public and physicians and diagnosed early, 2) treated effectively in order to optimize quality of life and minimize injuries, 3) has its pathophysiology fully understood, and 4) has its relevance to neurodegenerative disease characterized such that interventions can effectively delay the onset of or prevent the development of overt neurodegenerative disease (e.g., Parkinson' disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA)).

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Part II

RBD: Clinical Spectrum

Clinical Aspects of Idiopathic RBD

4

Laura Pérez-Carbonell and Alex Iranzo

4.1 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM sleep parasomnia characterized by vivid nightmares and dream-enacting behaviors during sleep that was formally described in 1986 [1]. The term dream-enacting behaviors has been used to describe episodes where individuals display movements during their sleep that presumably mirror the content of their dreams [1–5]. These symptoms are associated with excessive electromyographic activity during REM sleep in a polysomnographic study (PSG). The suspected pathophysiology of RBD relies on an underlying dysfunction of the lower brainstem nuclei that modulate REM sleep muscle tone and their anatomic connections [6]. As a consequence of the physiological higher amount of REM sleep in the latter half of the sleep period, RBD tends to be exhibited most prominently in the early morning hours, but not exclusively.

The idiopathic (or isolated) form of RBD (iRBD) is diagnosed in absence of any coexistent neurological condition (e.g., Parkinson disease (PD), narcolepsy, encephalitis, structural insult of the brainstem or limbic system), alcohol withdrawal, or the introduction of certain drugs (beta-blockers, antidepressants) [2, 7–12].

In contrast to other parasomnias, iRBD has significant ethical and medical implications (as discussed in Chap. 22) because the majority of patients with iRBD eventually develops a neurodegenerative disease, mainly PD and dementia with Lewy bodies (DLB) [13, 14], and those who remain disease-free during a long time of clinical follow-up show markers of neurodegeneration such as smell loss and decreased dopaminergic innervation in the putamen [15]. Therefore, a correct and early detection of individuals with iRBD is of crucial relevance, as will be discussed below.

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4.2 Epidemiology and Demographic Features

The actual occurrence of iRBD remains unclear in the general population. When PSG is performed, the estimated prevalence ranges between 0.3 and 1.15% in individuals over 60 years [16–18]. When using questionnaires, the prevalence in elderly people is estimated to be higher (4.6–7.7%) [19, 20]. These questionnaire studies without PSG confirmation overestimate the condition as a result of numerous false-positives likely related to cases of severe obstructive sleep apnea, NREM parasomnias (sleepwalking, sleep terrors), periodic limb movement disorder in sleep, and other conditions [3, 18].

iRBD is usually diagnosed in individuals over 50 years old [9–11, 21–23]. Nevertheless, the percentage of iRBD patients with an estimated (by clinical history but not confirmed by PSG) early age of onset (i.e. <50 years old) in some series has been set to be around 30–40% [24–28].

The majority of patients identified in sleep centers with the diagnosis of iRBD are men [3, 7, 22, 23]. The cause of such male predominance remains uncertain, and, in fact, a study evaluating circulating sex hormones in patients with iRBD [29] did not find abnormalities. Yet, iRBD is probably under-recognized in women [30], and this might be partly related to the fact that female iRBD patients tend to have less aggressive dream-enacting behaviors [21, 31–33]. In fact, sleep-related injuries related to iRBD are more common in men than in women [34]. Nonetheless, the proportion of affected women has increased by over 20% during the last decade [21], probably as a consequence of a better awareness of the condition among doctors. The risk, however, of phenoconversion to a neurodegenerative disease seems to be similar in men than in women [21]. (Chapter 16 covers the topic of gender implications in RBD.)

Several environmental factors have been identified to be associated with a higher risk of developing iRBD in the general population. Similar to what has been consistently shown in PD, head injury, occupational pesticide and solvent exposure, and farming are risk factors for iRBD. Also, in contrast to PD, smoking seems to be an iRBD risk factor, and there is no identified link between caffeine use and iRBD [23, 35]. However, these findings need to be confirmed by other studies. Other factors that appear to be protective in PD (e.g., Mediterranean diet, physical exercise) or have a detrimental effect (e.g., excessive consumption of dairy products or animal fat) have not yet been studied in iRBD patients.

Genetic factors may also play a predisposing role in the pathogenesis of iRBD. Familial aggregation is still a controversial issue in iRBD. There are no convincing familial descriptions of iRBD confirmed by PSG. The most common gene mutation in PD, LRRK2, is absent in iRBD [36]. However, GBA mutations occur in about 10% of subjects with iRBD [23, 37]. The C9orf72 mutation and several genetic loci (SCARB2, MAPT, GBA gene) have been found in iRBD patients in a higher rate than controls [38, 39]. These findings may suggest the presence of a genetic susceptibility in a small subgroup of iRBD patients. (Chapter 42 covers the topic of the genetics of RBD.)

4.3 Clinical Features

The clinical description of iRBD at presentation emerges from publications either focused on iRBD exclusively [3, 21] or from series of patients with both idiopathic and secondary forms of RBD [9–11, 40, 41].

The core symptomatology of iRBD involves abnormal behaviors during sleep, with unpleasant dreams, in the absence of any waking motor and cognitive complaints, and without any neurologic disorder being detected. Nonetheless, the reason why patients with iRBD attend a sleep center for the first time may not be related to these features. In some cases the reason for referral to a sleep center may be other sleep symptoms, such as hypersomnia, sleep disruption, or a clinical suspicion of sleep apnea [21, 40], and it is only specific questioning by a sleep doctor that unmasks a typical history of concomitant RBD [41]. In these cases, hypersomnia, insomnia, and apnea are not linked to iRBD, as they are simply coexistent unrelated conditions. Since about 50% of iRBD patients are completely unaware of their behaviors during sleep [21], interviews with bed partners are essential to obtain a detailed description of the RBD episodes. This has important implications for RBD screening and treatment response questionnaires, which based on these reported data should also include the input of the bed partner.

Although specific triggers are not normally depicted, some patients have linked the beginning of the symptomatology to a stressful situation. Several life events have been associated with the onset of iRBD, such as having a quarrel with a relative, being a victim of a fraud, receiving the diagnosis of cancer, having major cardiac surgery, having severe oral candidiasis, going through a divorce, being subjected to public humiliation, being in a car accident (without injury), and being involved in a natural disaster [7, 21]. Some patients believe that certain activities (e.g., watching a thriller before going to bed) may have an effect on triggering an RBD episode that same night [21].

Abnormal sleep behaviors (Table 4.1)**.** In iRBD, abnormal motor behaviors and vocalizations are comparably very common. RBD events appear abruptly, last from seconds to a few minutes, and, in the majority of cases, are confined to bed.

There is a wide spectrum of severity and complexity in the motor activities displayed by patients with iRBD, from simple jerks to highly elaborated movements. Body and limb jerks are the most common manifestations of iRBD, and do not seem to represent a dream but an abrupt startle in some instances. Given the primitive nature of some of the displayed jerky movements, it has been hypothesized that central pattern generators of archaic threat-simulating behaviors in the brainstem might take part in their origin [42].

In addition, aggressive dream-enacting actions are also common and include punching, kicking, hitting the nightstand, biting, and assaulting the bed partner. Falling out of bed is frequent in the iRBD population, although it is not very frequent in a single individual (e.g., a total of 1–10 falls during 3–10 years of RBD symptomatology). As a result, sleep-related injuries such as bruises, pulled hair,

Table 4.1 Abnormal sleep behaviors in 236 patients with polysomnography-confirmed idiopathic rapid eye movement sleep behavior disorder from the Multidisciplinary Sleep Unit of the Hospital Clinic de Barcelona, Spain

Self-awareness of sleep behaviors	*n* (%)	**128 (54.2)**
Motor behaviors		
Punching	*n* (%)	**203 (86.0)**
Kicking	*n* (%)	**195 (82.6)**
Falling out of bed	*n* (%)	**182 (77.9)**
Gesturing	*n* (%)	**172 (72.9)**
Knocking items off the nightstand	*n* (%)	**154 (65.2)**
Sitting up in the bed	*n* (%)	**88 (37.3)**
Getting out of the bed	*n* (%)	**56 (23.7)**
Assaulting the bed partner	*n* (%)	**49 (20.8)**
Biting	*n* (%)	**22 (9.3)**
Measures of protection in the bedroom	*n* (%)	**123 (52.1)**
Patients injured	*n* (%)	**138 (58.5)**
Bed partners injured	*n* (%)	**51 (21.6)**
Vocalizations		
Talking	*n* (%)	**224 (94.9)**
Screaming	*n* (%)	**212 (89.8)**
Moaning	*n* (%)	**147 (62.3)**
Laughing	*n* (%)	**124 (52.5)**
Crying	*n* (%)	**105 (44.5)**
Swearing	*n* (%)	**90 (38.1)**
Singing	*n* (%)	**32 (13.6)**
Barking	*n* (%)	**2 (0.8)**

lacerations, dislocations, fractures, and even subdural hematomas occur in a high percentage of patients or their bed partners (Fig. 4.1) [21, 43]. Patients who have experienced violent episodes tend to adopt protective measures (e.g., tying themselves to the bed, removing furniture, installing bed rails, or having a mattress or pillows placed on the floor next to their side) (Fig. 4.2) [7]. Furthermore, serious consequences with marital and forensic implications have also been reported in extreme cases [44, 45], highlighting the relevance to consider starting a treatment even in individuals with a low frequency of episodes [46].

Nonviolent behaviors where patients seem to perform elaborated activities, such as eating, trying to reach something, or giving a speech, can occur [47]. Other nonviolent behaviors are joyful such as singing, whistling, clapping, and dancing [48]. These semi-purposeful actions, along with the concurrent ability of patients to speak, suggest activation of the cerebral cortex. Fear, laughing, smiling, aggressiveness, and annoyance are facial expressions that may accompany the motor behaviors. The association of intense emotions suggests dysregulation of the limbic system.

About 25% of iRBD patients report getting out of the bed and even walking. However, these "out-of-bed" episodes are brief, and they are likely to represent confusional awakenings and not pure RBD events, since they predate the onset of cognitive impairment [21].

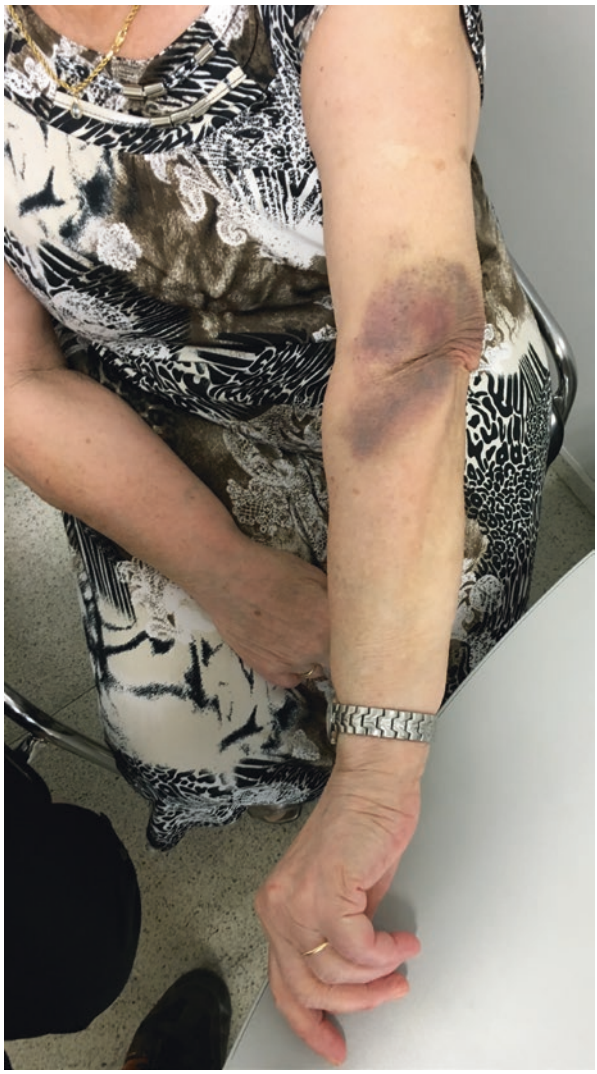

Fig. 4.1 Hematoma around the elbow after falling out of bed during a RBD episode

Fig. 4.2 Protective measures by placing pillows next to the nightstand and on the floor to prevent sleep-related injuries from RBD violent episodes

The existence of a specific pattern and profile of the motor actions displayed in episodes of iRBD has been assessed [48]. These movements seem to be faster, jerkier, and more repeated than the ones performed during wakefulness.

Vocalizations occur as part of the behavioral anomalies during sleep. In RBD, the emitted sounds may be loud and suggest unpleasant dream mentation [2]. Talking and screaming are the most frequent vocalizations. Patients may also swear, cry, or sing, although these are less commonly found [21]. When patients speak during an iRBD episode, the speech can be fluent and have an appropriate syntax, but in many cases, it is difficult to understand. Furthermore, the usage of a foreign language and the modulation of the voice depending on the content of the dream have been previously described [47]. In our personal experience in Catalonia, Catalan patients may speak in both Spanish and Catalan languages in a single episode of RBD.

According to the clinical history, the evolution of the clinical manifestations of iRBD may range from a stable to a progressive or fluctuating course over time and

even a complete remission of the symptoms. Nevertheless, once iRBD is established, video-PSG shows that the episodes usually occur almost on a daily basis, with night-to-night variability in their intensity [3]. Consequently, not only the sleep of patients but also the sleep of their partners may be disrupted, which might have a long-term impact on patients' intimate relationships [49].

Unpleasant dreams (Table 4.2)**.** Dreams in iRBD have unpleasant content. Only a small proportion of iRBD patients (5–10%) do not remember the content of their dreams. In those cases, the scenes where patients appear to be enacting unpleasant dreams are sometimes attested by the bed partner [3]. During RBD episodes, patients have their eyes closed in contrast to NREM sleep parasomnias. If awakened in the middle of an event of RBD, individuals are oriented and might or might not have recollection of a nightmare [50]. The perception of the dreams is usually intense and vivid and may be experienced as terrifying by some patients, while others do not seem to be affected at all. Surprisingly, the vast majority of iRBD patients often report a good night sleep, despite having a long history of nightmares and aggressive sleep behaviors [21].

The content of dreams, when recalled, frequently involves threatening situations where the patient is being attacked (the most recurrent theme among patients), or chased, usually by a stranger. Familiar people are less commonly involved. Arguing with someone and falling from a cliff are other recurrent themes. In contrast to what usually happens in NREM sleep parasomnias, the most common reaction of the iRBD dreamer to a dangerous situation or threat is to fight back instead of running away [7, 51]. iRBD patients commonly take action in their dreams, by adopting a self-defense attitude, and are not the provokers of the violent situations [7]. Attempts to protect a loved one from harmful situation are typical [7, 52]. Frightening situations include a wide variety of animals attacking, with dogs and snakes often involved, but dreams containing lions and bulls also seem to be present quite regularly. Monsters emerging from a lake or a cave may also occur. Sports-related intense situations, namely, soccer and other action-packed sports (e.g., boxing), may occur [21]. Dreams involving sexual elements and eating are not usually reported [53].

Situations based on the patients' past are sometimes part of the dreams in iRBD, but mundane concerns that patients might be thinking about during the day are not generally present. Interestingly, despite the violent and aggressive themes seen in these dreams, patients have no increased level of aggressiveness during wakefulness [53].

Overall, when comparing the symptomatology in iRBD and that in secondary neurodegenerative forms of RBD such as PD, DLB, and multiple system atrophy (MSA), similar behaviors and dream content are found [53, 54]. However, iRBD tends to be more aggressive and violent compared RBD with PD and MSA [54].

Table 4.2 Unpleasant dream recall in 236 patients with polysomnography-confirmed idiopathic rapid eye movement sleep behavior disorder from the Multidisciplinary Sleep Unit of the Hospital Clinic de Barcelona, Spain

Unpleasant dream recall	*n* (%)	**218 (92.4)**
Dream content		
Attacked by someone	*n* (%)	**186 (78.8)**
Arguing with someone	*n* (%)	**149 (63.1)**
Chased by someone	*n* (%)	**136 (57.6)**
Falling from a cliff	*n* (%)	**110 (46.6)**
Attacked by an animal	*n* (%)	**90 (38.1)**
Dog	*n* (%)	**32 (13.6)**
Snake	*n* (%)	**17 (7.2)**
Lion	*n* (%)	**10 (4.2)**
Bull	*n* (%)	**10 (4.2)**
Horse	*n* (%)	**5 (2.1)**
Insect	*n* (%)	**5 (2.1)**
Cat	*n* (%)	**4 (1.7)**
Rat	*n* (%)	**4 (1.7)**
Tiger	*n* (%)	**4 (1.7)**
Pig	*n* (%)	**3 (1.3)**
Wolf	*n* (%)	**3 (1.3)**
Crocodile	*n* (%)	**2 (0.8)**
Cow	*n* (%)	**2 (0.8)**
Mole	*n* (%)	**1 (0.4)**
Piranha	*n* (%)	**1 (0.4)**
Wild boar	*n* (%)	**1 (0.4)**
Action sports	*n* (%)	**35 (14.8)**
Soccer	*n* (%)	**28 (11.9)**
Boxing	*n* (%)	**2 (0.8)**
Skiing	*n* (%)	**1 (0.4)**
Basketball	*n* (%)	**1 (0.4)**
Motorcycling	*n* (%)	**1 (0.4)**
Cycling	*n* (%)	**1 (0.4)**
Children in a life-threatening situation	*n* (%)	**29 (12.3)**

The frequency and intensity of both the abnormal behaviors and unpleasant dreams in RBD can be decreased and even suppressed with bedtime melatonin and/or clonazepam therapy. However, there is no effect of these therapies in halting the progression toward a synucleinopathy.

Additional clinical features. Signs or symptoms that are characteristic of PD, DLB, and MSA, and that suggest an underlying neurodegenerative process, usually appear in patients with iRBD [15]. Some of these features are olfactory loss, depression, impaired color vision, dysautonomia, subtle parkinsonian signs, and asymptomatic cognitive dysfunction. Moreover, patients show the pathological substrate of PD (synuclein deposits in the peripheral autonomous nervous system, microglia

activation in the substantia nigra, and decreased dopaminergic content in the nigrostriatal system [55]).

4.4 Detection of iRBD

The diagnosis of iRBD includes clinical history and video-PSG. iRBD should be suspected when the clinical manifestations are frequent, vigorous, and affect individuals over 50 years of age. Identification of individuals with iRBD is often intricate, and underdiagnosis is common [16–18]. A number of reasons may be responsible for the difficulty in detecting iRBD cases. On the one hand, there is still a lack of awareness of the condition among clinicians [49]. While the diagnosis of RBD may easily come to mind in patients with a neurodegenerative syndrome (PD, DLB, MSA, mild cognitive impairment), clinical suspicion is rather challenging outside the neurological setting. On the other hand, patients with iRBD tend to defer seeking medical advice and have an estimated duration of the disorder at referral of at least several years [3, 49]. This delay may be a consequence of several reasons, namely, a perception of mildness or the transient nature of symptoms, a non-pathological view of the sleep behaviors, embarrassment, and unawareness when there is a lack of a witness [49]. However, in the largest published series describing the clinical characteristics of iRBD [21], an increasing amount of referrals was made in the last decade. In this study, the median interval between the estimated age of onset and age at medical consultation was 4 years [21]. Almost half of the patients were completely unaware of their actions during sleep. Some who were aware of them perceived the symptoms as a benign phenomenon and only decided to consult a clinician when the behaviors became violent, resulted in injuries, or persisted over the years.

The severity of symptoms seems to play a key role in the decision of consulting a clinician. Furthermore, prominent behaviors may be easily detected by spouses, who generally are of crucial importance in encouraging patients to request medical consultation [49], particularly when women are the bed partners [21]. Therefore, underdiagnosis of the disease may occur mainly in patients who are single, sleep alone, or have a mild form of iRBD that are not noticed by their bed partners [49].

When abnormal behaviors occur during sleep, other entities that may mimic RBD symptomatology should be considered. NREM sleep parasomnias, nocturnal seizures, severe obstructive sleep apnea, and severe periodic limb movement disorder can exhibit the same typical dream-enacting behaviors and unpleasant dreams seen in iRBD [57, 58]. (Chapter 26 covers the topic of RBD mimics.) The co-occurrence of RBD and some of these entities has also been described, namely, NREM sleep parasomnias (overlap parasomnia syndrome) [56], obstructive sleep apnea [21], periodic limb movements during sleep [59], and epilepsy [60].

4.5 iRBD as a Prodromal Manifestation of Neurodegenerative Diseases

iRBD often antedates the development of a neurodegenerative condition, namely, a synucleinopathy. Synucleinopathies are a group of diseases that include PD, DLB, and MSA. Their neuropathological hallmark is the deposit of abnormal phosphorylated alpha-synuclein that is present in neurons and, to some extent, in glial cells of the central nervous system. In PD and DLB, alpha-synuclein aggregates constitute Lewy bodies and Lewy neurites [61]. Postmortem studies have shown that in iRBD patients who developed mild cognitive impairment, PD, and DLB, there are deposits of alpha-synuclein in the autonomic and central nervous systems [62, 63]. In two patients with iRBD who died from unrelated causes, postmortem neuropathological studies showed the same, but less extensive, findings [64, 65]. In living iRBD subjects, biopsies of organs innervated by the peripheral autonomic nervous system show alpha-synuclein deposits in the colon, salivary glands, and skin [15, 66–69] (This topic is covered in Chap. 40).

In iRBD, involvement of structures beyond the nuclei that regulate REM sleep is responsible for the appearance of motor and nonmotor symptoms. Some of this symptomatology (e.g., constipation, olfactory loss, depression) is detected in the prodromal stage of the synucleinopathies, yet they are common in the general population as well. But iRBD is not very frequent in the general population, and the majority of subjects with iRBD develop PD or DLB. Therefore, iRBD should be considered a distinct and unique clinical condition that represents a synucleinopathy per se [70].

The occurrence of prodromal symptomatology of PD has been studied in patients with iRBD [71] (Table 4.3). Hyposmia, depression, and constipation are particularly frequent. However, the sequence for their appearance is highly heterogeneous, which may reflect the variability of the pathological changes in the nervous system [72]. Olfactory dysfunction occurs in 36–58% of patients with iRBD [73]. Depression is also frequent and may be related to dysfunction of the serotoninergic system in the brainstem as reflected by hypoechogenicity of the raphe nucleus [74]. Almost 30% of iRBD patients report depressive symptoms, nearly 20% are treated with antidepressants [75], and depressive mood seems to be an independent contributor to quality of life in iRBD [76]. Autonomic dysfunction is predominantly related to cardiovagal and adrenergic functioning; systolic blood pressure drop, orthostatic hypotension, constipation, urinary symptoms, or erectile dysfunction in men are frequent in iRBD [72, 77, 78]. Subtle motor symptoms and signs are more frequent in iRBD compared to controls [78], with hypomimia, hypophonia, and reduced arm swing being the first manifestations before conversion to full clinical parkinsonism [79]. They are important findings in the follow-up of iRBD cases, since resting tremor is rarely an initial feature in these patients, whereas the akinetic-rigid parkinsonian syndrome predominates [70, 80]. Despite the lack of cognitive complaints, neuropsychological testing is often abnormal in iRBD. The most

Table 4.3 Coexisting abnormalities in iRBD

1. **Clinical symptoms and signs**
1.1. Subtle parkinsonian signs
1.2. Olfactory impairment
1.3. Color vision impairment
1.4. Autonomic abnormalities (constipation, orthostatic hypotension, urinary symptoms, and erectile dysfunction)
1.5. Depression
1.6. Pareidolic responses
2. **Neuropsychological deficits** in visuospatial, executive, and verbal memory dysfunction
3. **Electrophysiological abnormalities**
3.1. Electroenecephalographic slowing in frontal, temporal, and occipital regions during wakefulness and REM sleep
3.2. Reduced heart rate variability during wakefulness and sleep
3.3. Esophageal motor impairment
3.4. Retinal nerve fiber layer thinning
4. Neuroimaging abnormalities
4.1. Reduced putamen and caudate dopaminergic uptake
4.2. Substantia nigra hyperechogenecity
4.3. Substantia nigra loss of dorsolateral nigral hyperintensity
4.4. Substantia nigra microglia activation
4.5. Basal ganglia connectivity dysfunction
4.6. Altered connectivity between the left substantia nigra with the left putamen and the right occipital lobe
4.7. Decreased fractional anisotropy and increased mean diffusivity in the midbrain and pontine nuclei that regulate REM sleep
4.8. Reduced neuromelanin signal intensity in the coeruleus/subcoeruleus area
4.9. Brainstem raphe hypoechogenicity
4.10. Decreased metaiodobenzylguanidine uptake
4.11. Hyperperfusion in the pons and right hippocampus and hypoperfusion in the frontal lobe
4.12. Abnormal metabolic network characterized by increased activity in the pons and hippocampus and decreased activity in occipital and temporal areas
4.13. Increased gray matter density in the hippocampus
4.14. Decreased gray matter thickness in the frontal lobe
5. Biological abnormalities
5.1. Alpha-synuclein aggregates in the autonomic nerve fibers that innervate the colon, salivary glands, and skin
5.2. Reduced intraepidermal nerve fiber density
5.3. Cerebrospinal fluid levels of oligomer alpha-synuclein range from low in iRBD to mild in Parkinson disease without dementia and high in Parkinson disease with dementia
5.4. The microRNA 19b is downregulated in the serum
5.5. Presence of single nucleotide polymorphisms SCARB2 and MAPT
5.6. Presence of GBA gene mutations
5.7. Absence of LRRK2 gene mutations
5.8. Genetic variants (KP876057, KP876056, NM_000345.3:c*860T>A, NM_000345.3:c*2320A>T) of the 3′untranslated region (3′UTR) of alpha-synuclein

affected domains are visual search abilities and visuoconstructional learning skills. Involvement of nonverbal logic, attention, and executive function is also observed [81]. This neuropsychological pattern is similar to the one found, albeit less severe, in manifest PD and DLB. Importantly, cognitive impairment progresses over time in individuals with iRBD until the development of mild cognitive impairment that precedes dementia [70, 82].

From the first series with long-term follow-up of iRBD cases, an important proportion of patients eventually showed prominent parkinsonian, cerebellar, or cognitive symptoms. The first reported conversion of 38% of patients, with iRBD to a parkinsonian disorder [83], increased up to 81% when the follow-up was extended to 13 years [13]. A similar increase of patients that converted to a neurodegenerative disease (from 45 to 82%) was seen in another series after 7 additional years of follow-up [70, 84]. The same findings were observed in other longitudinal series [22, 23, 85–87]. Therefore, from the moment of the diagnosis of iRBD, the risk for phenoconversion (i.e., for fulfilling the diagnostic criteria of a neurodegenerative condition) increases with time. The estimated risk for conversion is 33% at 5 years, 76% at 10 years, and 91% at 14 years, from the time of iRBD diagnosis [14]. A recent study determined the presence of several prodromal features in a cohort of individuals with duration of iRBD of more than 10 years [15]. Patients with long-standing iRBD more frequently showed smell loss, constipation, and mild parkinsonian signs than controls, and abnormal dopaminergic imaging was found in 82% of the cases. After decades of non-conversion, one might speculate that an alternative physiopathological mechanism may be causing the disorder; however, the results of the study suggest the presence of an underlying neurodegenerative process even in patients who remain disease-free for a long period of time [15]. This heterogeneity of conversion timelines is one of the curious and as-yet unexplained features of iRBD.

PD and DLB are the predominant diagnoses evolving from iRBD. However, mild cognitive impairment may also emerge, and a small number of patients develop MSA. DLB is almost always preceded by mild cognitive impairment. Conversely, iRBD cases that develop mild cognitive impairment evolve to DLB and sometimes to PD. Phenoconversion from iRBD to other neurodegenerative disorders such as Alzheimer's disease (AD), progressive supranuclear palsy, corticobasal degeneration syndrome, spinocerebellar ataxias, or narcolepsy is extraordinarily rare. Two cases with neuropathology have been reported involving RBD and AD, with autopsy findings determining the final diagnosis of the Lewy body variant of AD, i.e., combined synucleinopathy-tauopathy [63]. Therefore, it is possible that most clinical cases of RBD with the clinical diagnosis of AD may indeed represent the neuropathological Lewy body variant of AD or Lewy body pathology alone.

The median age of RBD patients when the diagnosis of a neurodegenerative disease is established is around 75 years [3], with an interval from iRBD diagnosis to the diagnosis of a neurodegenerative disease of 7–14 years [13, 14]. However, the latent period from estimated RBD onset (by clinical history) until the development of parkinsonism or dementia is variable and can last for up to 50 years [13, 26].

The precise contribution of certain features for the conversion from iRBD to a neurodegenerative disease has been assessed in several studies. The most important determinant is time from iRBD diagnosis by vPSG. Olfactory loss, abnormal color

vision, subtle motor symptoms [87], impaired neuropsychological tests [82], the combination of hyperechogenicity of the substantia nigra with abnormal DAT-SPECT [88], and abnormal DAT-SPECT alone [22, 89] are risk factors for short-term conversion (2–5 years) to a clinically defined synucleinopathy. Increased delta and theta activity in occipital and central regions in electroencephalography (during wakefulness and REM sleep) is seen in patients with iRBD who develop mild cognitive impairment and later dementia [90, 91].

The following abnormalities worsen over time in iRBD: parkinsonian symptoms [79], neuropsychological deficits [92], tonic and phasic muscle activity during REM sleep assessed by PSG [93], and striatal dopaminergic uptake measured by dopamine transporter imaging [94]. In contrast, smell loss [95–97], dysautonomic features such as constipation [78, 98], and hyperechogenicity of the substantia nigra [99] remain stable over the years (Table 4.4).

Given the large amount of evidence proving that iRBD represents an early feature of a neurodegenerative disease, the more conservative term "cryptogenic" or "(clinically) isolated" RBD was suggested [100, 101, 102]. It seems that, with sufficient time, the totality of patients with iRBD would end up clinically diagnosed with a synucleinopathy, with a small minority being diagnosed with Lewy body disease at autopsy despite the final clinical diagnosis of iRBD. Even in apparently idiopathic cases, neuroimaging markers or pathological evaluation reveal evident signs of an underlying neurodegenerative process (e.g., synuclein deposition, microglia activation, reduced of dopamine content). Yet, since a specific etiology of RBD in humans remains uncertain, the term idiopathic is still often used to describe a patient with such a parasomnia, despite the presence of biological markers of neurodegeneration but not yet fulfilling the current clinical diagnostic criteria of a neurodegenerative disorder. (Chapter 36 covers the topic of biomarkers of neurodegenerative disease in iRBD.)

Table 4.4 Relevance of coexistent biomarkers in iRBD

1. Biomarkers that predict short-term risk of synucleinopathy conversion
1.1. Subtle signs of parkinsonism
1.2. Olfactory loss
1.3. Abnormal color vision
1.4. Combination of hyperechogenicity of the substantia nigra with reduced nigrostriatal dopaminergic binding in the striatum
1.5. Reduced nigrostriatal dopaminergic binding in the striatum alone
1.6. Impaired neuropsychological tests
1.7. Increased delta and theta activity in occipital and central regions in electroencephalography
2. Biomarkers that progress over time
2.1. Signs of parkinsonism
2.2. Neuropsychological deficits
2.3. Tonic and phasic muscle activity during REM sleep
2.4. Striatal dopaminergic uptake
3. Biomarkers that remain stable over time
3.1. Smell loss
3.2. Dysautonomic features
3.3. Hyperechogenicity of the substantia nigra

4.6 Follow-Up Strategy and Information Shared with the Patient

Several approaches may be chosen in the follow-up of patients with iRBD [3]. The best strategy remains a debated issue. One option consists of offering regular visits with a neurologist or a sleep specialist with expertise in neurodegenerative diseases. Doctors following patients with iRBD should be familiar with the condition and have broad knowledge about the clinical presentation of synucleinopathies at their initial stages. This implies that a physician should regularly perform neurological examinations to detect early signs of a neurodegenerative condition, including parkinsonism, mild cognitive impairment/dementia, and cerebellar syndrome. This would allow prompt discussion about the advisability of implementing symptomatic therapy (e.g., dopaminergic agents for parkinsonism, rivastigmine, or donepezil for cognitive impairment). When clinical examinations are normal, additional investigations (neuroimaging, neuropsychological evaluations, smell tests, etc.) are not needed at baseline or during follow-up visits since they do not change the prognosis and clinical evolution of the condition. However, there are ancillary tests that allow detecting iRBD individuals with increased risk of short-term conversion (e.g., hyposmia, abnormal DAT-SPECT), which would be a useful strategy for patient selection in future neuroprotective trials, when they become available.

To what extent clinicians should inform patients about the possibility of developing a neurodegenerative disease is a controversial matter [103]. Some physicians would argue that with a lack of a preventive or disease-modifying therapy there is no benefit for the patient in having the information. Also, it might be claimed that the disclosure may lead to an unnecessary disturbance of the person's normal life and that the patient could be anxiously waiting for a disease that may emerge in 10 or more years or never. However, a protective attitude is not necessarily a valid justification to avoid sharing information and runs against an individual's principle of autonomy. Patients have the right to know the long-term implications of iRBD, as with any other medical disorder. Moreover, after the diagnosis of iRBD is given, some of the patients or their relatives may look for information related to the disorder through other sources (especially the Internet) and realize that important information was withheld, with the consequent risk for major damage of the doctor-patient relationship. (This topic is also covered in Chap. 22 on clinical RBD vignettes.)

Regarding how to communicate the prognostic risk to iRBD patients, some points have been mentioned in a recent paper [104]: physicians may avoid mentioning the specific risk or rate of progression but rather express the prognostic estimation in broad terms; communication should be tailored according to patient's personality, background, education, age, and comorbidities; and the patient should always feel supported by the doctor, who must provide all the required care. A reasonable approach could begin by asking the patient whether he or she is interested in getting all the information related to the diagnosis of iRBD. If the patient is willing to know, then a discussion about the risk of suffering from a future neurodegenerative disorder should take place, along with information related to the current research efforts in identifying neuroprotective agents and in designing

neuroprotective studies to halt or slow down the neurodegenerative process. In follow-up visits, doctors should be solicitous in addressing any worries and misconceptions that may have roused the patient after the initial conversation [3]. Of course, routine follow-up visits also include the assessment of RBD symptomatology when specific therapy (e.g., clonazepam, melatonin) is implemented.

Conclusions

iRBD presents a wide clinical phenotypical heterogeneity. Clinicians should be aware of such variability at presentation in order to correctly detect the disorder. The lack of awareness of symptoms among patients is a striking and noteworthy feature. In this sense, spouses play a significant role in the decision of seeking medical consultation and are an invaluable source of clinical information. Bed partners should be encouraged to attend to all medical appointments with patients and to participate in all RBD-related questionnaires.

The well-established link between iRBD and the synucleinopathies is of clinical and scientific relevance. iRBD emerges as a highly specific prodromal marker of synucleinopathy neurodegeneration. Physicians following iRBD cases should look carefully for initial motor and cognitive signs and symptoms that patients may develop over time; this would allow doctors to correctly diagnose and manage, from the initial stages, a neurodegenerative condition. iRBD patients are a unique group to be selected for neuroprotection trials; in this regard, the latency period of often several years from iRBD diagnosis to disease diagnosis is an optimal window that could facilitate the introduction of putative therapies that may act to prevent or slow down the progression toward overt neurodegeneration.

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REM Sleep Behavior Disorder Associated with Parkinson's Disease and Multiple System Atrophy

5

Friederike Sixel-Döring and Claudia Trenkwalder

> *"... In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm. ... but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hanging, but even the floor and sashes of the room. …".*
>
> (James Parkinson, 1817) [1]

5.1 RBD in Parkinson's Disease

In his seminal "Essay on the Shaking Palsy", James Parkinson recognized sleep disturbances as part of the clinical syndrome that was to be later named after him. The observed phenomena possibly represent the first description of REM sleep behavior disorder (RBD) in Parkinson's disease (PD). However, for the larger portion of the ensuing two centuries, medical research focused on motor symptoms and the pathology of the substantia nigra, as this was regarded as the key to understanding the disease and creating successful treatment strategies for alleviating tremor, akinesia and rigidity. Over the last three decades, however, the first evidence of

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idiopathic RBD converting into PD was detected, and RBD was proposed as a precursor to neurodegenerative disease [2]. These findings opened a window into a better understanding of PD pathology. Together with data on the prevalence and clinical impact of sleep problems in PD [3, 4] and reports on sleep-related violence in PD [5, 6], they also kindled a successful new collaboration of movement disorder neurologists and sleep specialists. Sleep disorders and non-restorative sleep are now recognized as part of a non-motor symptoms complex with a significant impact on quality of life in PD patients and their caregivers [7–9]. Moreover, 81% of patients originally diagnosed with idiopathic RBD (iRBD) had developed Parkinsonism and/or dementia approximately 14 years after onset of RBD [10]. Other study groups confirmed these findings of RBD preceding PD by more than a decade, with a neurological disease-free survival rate from time of iRBD diagnosis of 65.2% at 5 years and 7.5% at 14 years [11–13].

Serial presynaptic dopamine transporter scintigraphy (DAT Scan) demonstrated a progressive loss of striatal tracer uptake in patients with iRBD [14]. F-fluorodeoxyglucose positron emission tomography (FDG-PET) metabolic patterns in iRBD were shown to closely resemble those of early PD patients [15]. Consequently, RBD is now recommended as a biomarker in clinical cohorts investigating prodromal PD (for an overview see [16]). Furthermore, iRBD may evolve to multiple system atrophy (MSA) or dementia with Lewy bodies (DLB) and only rarely to Alzheimer's disease or any tauopathy [11–13, 17, 18]. Lewy bodies and Lewy neurites as the histopathological hallmark of PD, multiple system atrophy (MSA) and DLB contain aggregated α-synuclein. Autopsy studies on patients originally diagnosed with iRBD showed evidence of neurodegenerative disease in 170 of 172 cases. An overwhelming majority (94%) of these patients were neuropathologically classified with a synucleinopathy [19], thus linking RBD to the misprocessing of α-synuclein with the appearance of Lewy bodies, although neuropathologically confirmed Lewy bodies may be incidental and not necessarily fully consistent with the clinical picture of a neurodegenerative disorder in an individual subject during his/her lifetime. However, the hypothesis that RBD is one of the most important premorbid markers of neurodegenerative disease with α-synuclein is generated from the long-term follow-up of patients with severe, often violent, RBD. The following overview attempts to compile what we know about the occurrence and clinical relevance of RBD in clinically manifest PD and MSA.

5.1.1 The Evolution of RBD in Early PD

Manifestation of motor symptoms such as rigidity, resting tremor, akinesia (often with an asymmetrical presentation) and later on postural instability, together with a positive response to levodopa, defines the diagnosis of PD according to UK Brain Bank criteria [20]. Reduction of facial expression, shuffling gait, reduced arm swing, micrographia and reduced fine motor dexterity are considered further typical signs of the disease. These symptoms relate to the well-established dopamine deficiency that is due to substantial degeneration of dopaminergic neurons in the substantia nigra. Consequently, substitution of the dopamine precursor levodopa will, at least in the early stages of manifest motor disease, lead to an almost complete

restoration of motor function. The continued alleviation of motor symptoms with levodopa and the emergence of fluctuations and dyskinesias are regarded as pathognomonic for the so-called prototypical PD. At the beginning of our millennium, pathoanatomical studies by Braak and collaborators led to the development of a staging system for PD. This is based on the topographical and temporal progression of α-synuclein containing Lewy bodies and neurites from olfactory structures and the medulla rostral to the pons, midbrain and substantia nigra, spreading to limbic structures and lastly the neocortex [21]. This staging model is currently widely accepted because it embraces premotor and prodromal disease features as well as disease progression in later stages, although it may not explain the variety of PD phenotypes.

Data from animal experiments underlines the role of the ventral mesopontine junction (VPM-J) for the control of sleep time and muscle activity during sleep, showing that a lesion in the caudal part of VPM-J leads to motor activity during REM sleep closely resembling that of human RBD [22]. As the VPM-J is located close to the substantia nigra, it has been hypothesized that the progression of RBD to Parkinsonism is related to the spread of damage from the VPM-J to the substantia nigra [22]. At the time of motor manifestations of PD, pathoanatomical Braak stage 3–4 has already been reached. Following what we know about the ascension of Lewy body pathology and the regulation of REM sleep/REM sleep muscle atonia, one would suppose that the overwhelming majority of these newly diagnosed PD patients would present with RBD. However, a recently published meta-analysis on the prevalence of RBD in newly diagnosed PD patients (a total of 2462 patients and 3818 healthy controls in 8 studies) demonstrated an overall mean prevalence of RBD in newly diagnosed PD of 23.6% (range 4.3–69.4%) [23]. The fact that due to assessment methods RBD diagnosis was considered only "probable" in five out of the eight studies included in the meta-analysis may explain the wide range of prevalences given.

The one study using video-polysomnography (vPSG) for RBD assessment identified 25% of a de novo PD patient cohort with RBD [24]. Of note, none of the patients in this cohort were pre-diagnosed with RBD, and results from validated RBD screening instruments showed poor sensitivity and specificity. Another 26% of patients were seen with minor motor behaviors and/or vocalizations that did not meet the diagnostic criteria for RBD or even REM sleep without atonia (RWA) [25]. These phenomena were labelled as REM behavioral events (RBE) and were shown to correspond to dreaming [26]. vPSG follow-up data revealed an increase in the prevalence of RBD to 43% after 2 years; all patients with RBD at baseline continued to show RBD, and 38% of those originally diagnosed with RBE had converted to manifest RBD, leading to the hypothesis that RBE may be prodromal RBD [27].

This concept is supported by preliminary data from an ongoing longitudinal vPSG study from Bologna, where video analysis revealed similar findings of RBE and transition to manifest RBD over time (Provini and Sixel-Döring, in preparation). A similar issue has been described for isolated RWA; electromyographic measures increased over time, and transition to RBD occurred in 7% of otherwise healthy study subjects [28]. As 71% of these subjects also scored positive for at least one marker for impending neurodegenerative disease, such as cognitive impairment, finger speed deficit, impaired colour vision, olfactory dysfunction, orthostatic

hypotension and/or substantia nigra hyperechogenicity, longitudinal cohorts are necessary to establish the role of both prodromal RWA and prodromal RBD.

Although subgroup analysis of motor and cognitive features failed to establish a specific PD phenotype associated with RBD in this cohort of early PD patients [24, 27], another study group presented 3-year follow-up data of de novo PD patients at baseline and identified RBD as a predictor of earlier cognitive decline [29].

5.1.2 The Clinical Phenomenology of RBD in PD

Various visual classification systems have attempted to describe and characterize REM sleep-associated dream-enacting behaviors with the aid of the video recordings synchronized to the polysomnography (PSG). Some differentiate between simple and complex movements [30, 31] or rate RBD manifestations as mild, moderate or severe according to the behaviors visible [17]. Others used qualitative descriptions and elaborate electromyographic measurements [32, 33] or detailed video analysis of the number, duration and type of motor events during REM sleep [34]. The REM sleep behavior disorder severity scale (RBDSS) [35] uses phenomenological categories such as the localization of movements—distal, proximal or axial—and the presence or absence of vocalizations (Table 5.1) with the final RBD severity score being determined by the most severe episode observed during one night.

Descriptive video analysis demonstrated that PD patients with RBD mostly show minor/mild motor events during REM sleep, with only 3.6% of all RBD episodes observed being judged as violent [34]. Another study identified violent behaviors in only 15.6% of PD patients with RBD [17]. In a study using the RBDSS [36], 30%

Table 5.1 REM sleep behavior disorder severity scale (RBDSS) [52]

Motor events	Vocalizations
0. = no visible motor activity, RWA present Only definition criteria of RWA according to ICSD are fulfilled, no other phasic muscle activity in the limbs or face is visible or obvious on recording **1. = small movements or jerks** Isolated, single hand or foot movements or facial jerks visible, restricted to the distal extremities and/or face **2. = proximal movements including violent behavior** Single movements or series of movements including proximal extremities, no change of position **3. = axial movements including bed falls** Movements with axial involvement and/or change of body position, falls	**.0 = no vocalization** Snoring with some sound may be present and should be differentiated from REM-associated vocalization **.1 = all sleep-associated sounds other than respiratory noises** Talking, shouting, murmuring, laughing and screaming, either tonic or phasic, are present during at least one REM episode

ICSD International Classification of Sleep Disorders, *RWA* rapid eye movement (REM) sleep without atonia

of PD patients with RBD showed movements involving the trunk and changes of body position with the risk of bed falls and thus fulfilled criteria for violent, potentially harmful behaviors. Thirty-eight percent of the patients showed proximal limb involvement. Another 32% of PD patients were identified with only mild, non-violent manifestations of RBD in the distal extremities or the face. Vocalizations were present in 59% of the patients in the study. Their occurrence increased with RBD severity and was found to be highest in the group of PD patients who had axial involvement. In only 7% of the patients vocalizations were the sole manifestation of RBD during the night investigated. However, a comparative study of PD patients with RBD demonstrated that in 60% of patients investigated with vPSG on consecutive nights, the occurrence as well as the phenomenology of dream-enacting motor events in PD showed a considerable night-to-night variability in the individual patient [35], ranging from mild distal jerks and gestures in one night to thrashing and axial movements with the risk of falling out of bed or hurting the bed partner in the other night. Predictors or risk factors for violent RBD manifestations in PD are currently not known. These aspects need to be considered when counselling on RBD, its implications for nocturnal safety and potential pharmacotherapy. The night-to-night variability also leads to the question of how many nights are needed to definitely diagnose clinical manifestations of RBD in a patient. However, as electromyography (EMG) scores have not been shown to differ on two consecutive nights, one night of PSG may suffice if careful video analysis is combined with EMG criteria [37, 38].

Due to a lack of longitudinal vPSG-supported data, we currently do not have sufficient knowledge about the natural course of RBD severity as PD progresses, i.e. whether late-stage PD patients still continue to exhibit the same amount and phenotype of RBD manifestations as in the early stage of PD. Clinical observations suggest a possible modification of the RBD symptomatology during the course of the disease. In early stages the amount of RWA has been shown to increase over time even in PD patients without RBD [27], as if the ability to produce REM muscle atonia is lost with disease progression. Figures 5.1 and 5.2 depict the polysomnographic changes in RWA from the de novo stage to an advanced stage of PD with RBD; whereas the de novo patient mainly shows phasic EMG activity, the more advanced patient seems to have lost the ability to produce atonia during REM sleep, with continuous tonic EMG activity and additionally superimposed phasic activity.

Another unresolved question concerns the origin of REM-associated motor behaviors. In three studies using video analysis of RBD in PD patients [35, 36, 39], the behavioral patterns observed during RBD episodes showed remarkably restored motor control with fluid, fast, even forceful movements and thus quite in contrast to the slow, often restricted Parkinsonian movement pattern during wakefulness. Speech, however, remained mostly unintelligible. These findings imply a REM sleep-related disjunction of pyramidal and extrapyramidal motor systems where movements during RBD episodes are generated by the motor cortex and follow the pyramidal tract, bypassing the extrapyramidal pathways [39].

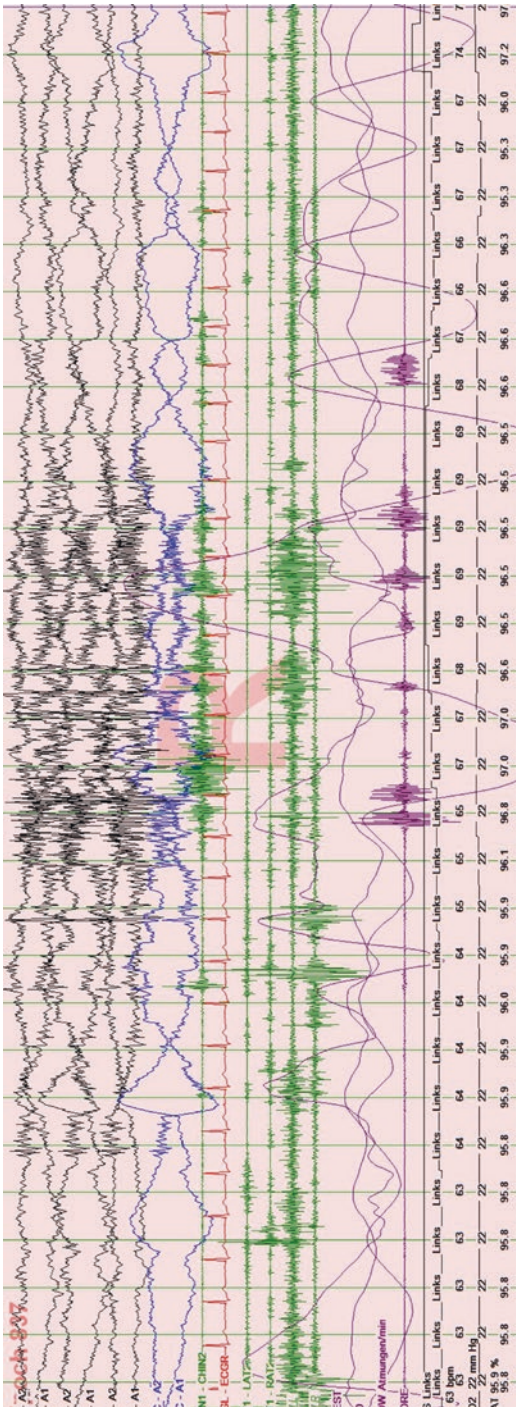

Fig. 5.1 Polysomnography screenshot showing a REM sleep epoch of a de novo Parkinson's disease patient with REM sleep behavior disorder. EMG sensitivity for chin and both Mm. flexor digitorum superficialis ("Arm L" and "Arm R") set at 5 μV/mm. Time basis set at 1 s/div with 30 s/page. Note excessive amounts of phasic muscle activity in chin and both Mm. flexor digitorum superficialis. Patient is trashing with the arms and talking

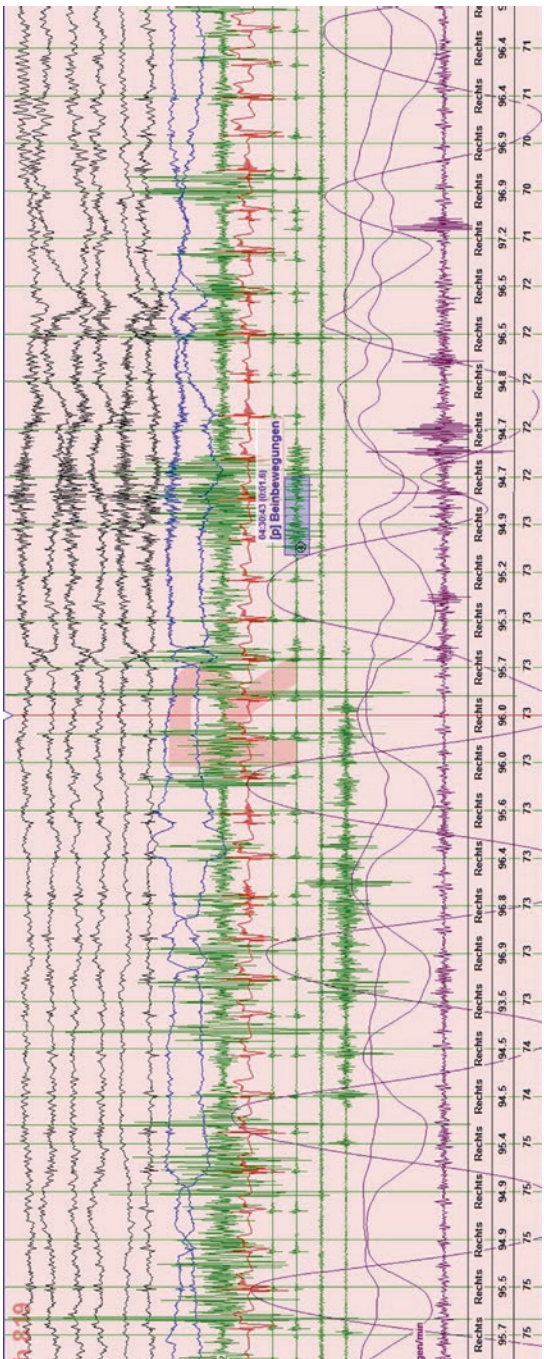

Fig. 5.2 Polysomnography screenshot showing a REM sleep epoch of an advanced Parkinson's disease patient with REM sleep behavior disorder. EMG sensitivity for chin and both Mm. flexor digitorum superficialis ("Arm L" and "Arm R") set at 5 μV/mm. Time basis set at 1 s/div with 30 s/page. Note excessive amounts of tonic and superimposed phasic muscle activity in chin as well as increased phasic muscle activity in both Mm. flexor digitorum superficialis ("Arm L" and "Arm R"). Patient is mumbling and boxing

5.1.3 RBD in Advanced PD

Violent behaviors of RBD in PD can occur at any time during the course of the disease and are not related to either the early or advanced stage of PD. As PD progresses, nocturnal disturbances with abnormal, disruptive and injurious behaviors resulting from RBD, in addition to frequent awakenings due to akinesia or restless legs syndrome, may bother the patient and substantially add to the caregiver's burden. A questionnaire-based study revealed that 15% of consecutive PD patient/caregiver pairs in an outpatient clinic reported the experience of sleep-related injuries, with RBD as a probable cause in 66% of PD patients [5]. PD patients on dopaminergic medication may exhibit a variety of nocturnal motor and non-motor behaviors such as confusional states, hallucinations and/or severe periodic leg movements in sleep (PLMS), which can be mistaken for RBD when relying on patients' history alone. Critical issues on the usefulness of the RBD screening questionnaire (RBDSQ) have not only been raised by the aforementioned study [24] in early PD patients, but RBDSQ validation studies in more advanced PD patients [38, 40] have also raised issues on its usefulness and applicability in patients with a clinically manifest Parkinsonian syndrome, as sensitivity and specificity varied, strongly depending on the clinical context. These findings are in line with recent results from a further study on questionnaire-based RBD detection with the RBDSQ in sleep-disordered non-PD patients and healthy controls [41], calling for a reappraisal and revision.

A predominant feature of RBD consists of an increased amount of vivid dreams, which can often be recalled by the patient [6] and may perhaps prove a more accurate screening tool for RBD. At present, vPSG is mandatory for establishing a definite RBD diagnosis in PD [42, 43], and differentiating RBD from nocturnal hallucinations or confusion is essential for choosing adequate therapy. In the largest cross-sectional cohort of sleep-disturbed PD patients investigated with vPSG so far, the frequency of RBD was determined at 46% [44]. Older age, longer disease duration, a higher Hoehn and Yahr stage, a higher daily dose of levodopa, more falls, more fluctuations and a higher rate of psychiatric comorbidity were identified as associated factors. These findings are in line with other studies [45–48], suggesting that the appearance of RBD during the course of PD may be a predictor of entering a more advanced stage of the disease. In addition, recent cross-sectional studies provided evidence that PD patients with RBD tend to have specific motor and non-motor manifestations such as autonomic dysfunction including orthostatic hypotension, impairment of colour vision [49] and freezing of gait [50].

The aforementioned observations in early PD, pathological and neuroimaging studies and studies on biomarkers and non-motor symptoms align to the clinical phenomenology of PD with a high heterogeneity of early features and later outcomes of the disease. This has led to a recently published new concept proposing three possible routes of spread of pathology in PD, namely, a brainstem route with early sleep dysfunction such as RBD and dysautonomia; an olfactory-to-limbic route with depression, fatigue, central pain and weight loss; and lastly a neocortical subtype with early cognitive symptoms, anxiety, apathy and falls (for an overview see [51]). A recent study using diffusion magnetic resonance imaging (MRI)

connectometry and calculation of quantitative anisotropy showed microstructural white matter changes in the bilateral cingulum pathways, corpus callosum, bilateral inferior fronto-occipital fasciculi, bilateral corticospinal tracts and the middle cerebellar peduncles specific to PD patients with RBD [52, 53]. These findings support the concept of different pathological pathways leading to different phenotypes of PD. If this concept proves true, objective biomarkers will have to be evaluated in future long-term cohorts.

5.2 RBD in Multiple System Atrophy (MSA)

MSA presents in two clinical variants, namely, MSA Parkinson type (MSA-P) with a primarily Parkinsonian syndrome and MSA cerebellar type (MSA-C) with predominantly cerebellar symptoms. Similar to PD and DLB, both variants are characterized by the pathological accumulation of α-synuclein in specific brain areas. Whereas in PD and DLB α-synuclein aggregates in neurons, forming the aforementioned Lewy bodies and Lewy neurites, insoluble α-synuclein forms glial cytoplasmic inclusions inside oligodendroglia as a corresponding pathological hallmark of MSA [54]. In the clinical setting, MSA-P in particular may at first present with symptoms very similar to prototypical PD. The sporadic, progressive adult-onset disorder of currently unknown etiopathogenesis is defined by consensus criteria [54], comprising autonomic failure, poor levodopa-responsive Parkinsonism or cerebellar ataxia and/or supporting neuroimaging abnormalities. Rapid disease progression marks MSA as a sort of "fast-track PD" without the benefit of symptomatic dopaminergic therapies to reduce the burden of the disease. The first systematic PSG study in MSA identified RBD in 90% of patients [55]. A more recently published cross-sectional PSG study combined with a meta-analysis of previous studies found a prevalence of RBD of 88% in MSA patients [56]. Both studies conceded that many patients report symptoms of RBD before the onset of motor deficits. In one study 5% of the patients with idiopathic RBD who had converted to neurodegenerative disease within a mean of 5.1 years were clinically classified with MSA [11]. These findings allow for the conclusion that, similar to prototypical PD, RBD may be a premotor manifestation of MSA.

Comparative PSG studies in PD and MSA patients showed no qualitative differences in RBD-related symptoms detected by video or on the PSG recordings [17, 57]. However, patients with MSA had a higher percentage of RWA, a greater index of PLMs and less total sleep time compared to PD patients, suggesting a more severe dysfunction in the structures modulating sleep [17]. Similar to PD, MSA patients also showed a transient disappearance of Parkinsonian motor symptoms with normalization of movement patterns during RBD episodes [58, 59]. However, an attempt to differentiate MSA-P and MSA-C with vPSG and movement analysis failed, showing equally disturbed sleep profiles in both cohorts as a probable indicator of similar pathologic mechanisms [59, 60].

Data from retrospective sleep interviews on the evolution of RBD in MSA suggest that in the majority of patients, RBD occurs prior to, or at the onset of, the motor manifestation of the disease and then disappears, with RBD symptoms remaining

mostly non-violent or even silent [57]. Unfortunately, cohorts of MSA patients followed over several years are not available to document the evolution of RBD over the course of the disease, and longitudinal vPSG-supported data are currently nonexistent. A single case study reported a decreased frequency of elaborate motor behaviors during REM sleep over time, in correlation with predominant tonic chin EMG activity, possibly as a sign of increased rigidity as the disease progressed [58]. In another two cases, the transition of originally idiopathic RBD to MSA with RBD was documented by vPSG, showing a diminished frequency of RBD episodes during the course of the disease accompanied by increasing abnormalities in the patients' sleep with nearly continuous motor and verbal behaviors and rapid oscillations of stage-determining PSG features, consistent with the concept of status dissociatus [61]. These observations support the hypothesis that the severity of the neurodegenerative process is mirrored in the increasing destruction of physiological sleep macrostructure.

In a recently published case series, five of eight patients (63%) with pure autonomic failure (PAF) were identified with RBD [62]. Of note, all patients met strict clinical criteria for PAF by reporting autonomic symptom duration for >5 years (mean 11.2 years) without any sign of motor or cerebellar involvement. In contrast to patients with MSA, dream-enacting behaviors manifested well after the PAF diagnosis, with an average time delay of 7.1 years. These findings suggest that PAF may represent a mild form of CNS α-synucleinopathy, as indicated by autopsy reports of Lewy bodies not only in postganglionic sympathetic neurons but also in the locus coeruleus and substantia nigra [63].

5.3 Concluding Remarks

Patients diagnosed with violent RBD in sleep centres have a high risk of converting to manifest neurodegenerative diseases within years or decades, associated with the misprocessing of α-synuclein over time. Presently, it is not possible to predict in patients with RBD whether they will develop prototypical PD, DLB or MSA. In PD, the ascending spread of Lewy body pathology from the REM sleep regulating medullar and pontine centres to the substantia nigra, as described by the Braak staging system, fits with the concept of RBD as a premotor manifestation of the disease and may thus be termed as prodromal PD. When using vPSG for the diagnosis of RBD in accordance with the currently valid diagnostic criteria for RBD as defined by the International Classification of Sleep Disorders, 3rd version, 25% of newly diagnosed PD patients actually show RBD. Recently, RBE, as dream-associated motor behaviors and/or vocalizations prodromal to full-blown RBD, have been described in de novo PD patients. In contrast to iRBD, the clinical manifestation of RBD in PD patients includes mostly mild to moderate motor behaviors. Violent and potentially injurious dream enactments are present in only 15–30% of patients. Although a considerable night-to-night variability of RBD severity in PD has been demonstrated, it is currently not clear whether the dream-enacting features of RBD may eventually disappear in later disease stages, as described for MSA. Clinical features and neurophysiologic measures of RBD do not differ between prototypical PD and MSA or between the two known types of MSA. Although clinical evidence that RBD predicts a specific clinical course of PD is not yet driven by sufficient

longitudinal data, results from large PD cohorts underline the role of RBD as a marker for entering a more advanced stage of the disease.

Note Added in Proof: A recently published study merits inclusion, along with its accompanying Editorial: (1) Pagano G, De Micco R, Yousaf T, Wilson H, Chandra A, Politis M. REM behavior disorder predicts motor progression and cognitive decline in Parkinson disease. Neurology 2018 Aug 8; doi: 10.1212/WNL.0000000000006134. (2) Mahowald MW, Schenck CH. The "when" and "where" of α-synucleinopathies: Insights from REM sleep behavior disorder. Neurology. 2018 Aug 8; doi: 10.1212/WNL.0000000000006129.

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REM Sleep Behavior Disorder Associated with Dementia with Lewy Bodies

6

Bradley F. Boeve

6.1 The RBD-DLB Association

RBD has been associated with numerous cases of dementia with Lewy bodies [1–36]. Additionally, several reports involving idiopathic RBD patients followed prospectively (and see below) have shown that phenoconversion to DLB occurs with equal, and perhaps greater, frequency than Parkinson's disease.

6.2 RBD and Diagnostic Criteria for DLB

The classic clinical features of spontaneous parkinsonism, recurrent and fully formed visual hallucinations, and fluctuations in cognition have been the "core" criteria for DLB since the original diagnostic classification system was developed [29, 37, 38]. The presence of two or more of these three core criteria satisfied the diagnosis of clinically probable DLB, and one of these criteria was fitting for clinically possible DLB [38]. The data available at the 3rd Consensus Conference for the Diagnostic Criteria for DLB led to the inclusion of RBD as a "supportive" criterion for DLB, which meant that the presence of RBD plus only one of the core criteria was sufficient for the clinically probable DLB designation [38].

A considerable body of additional evidence supporting the association of RBD plus DLB, regardless of other coexisting features, had accumulated after 2005 when the 3rd criteria were published [10–13, 15, 19, 21, 23–25, 28, 29, 32–35, 39, 40]. This elevated the presence of RBD as a fourth core feature for the diagnosis of DLB in the recently published 4th Consensus Conference for the Diagnostic Criteria for DLB [30]. There was ample debate among the panel of coauthors on whether PSG confirmation of RBD should be required for the RBD criterion or whether a strong

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Table 6.1 Key elements of the updated criteria for the clinical diagnosis of dementia with Lewy bodies

Presence of dementia
• Deficits on measures of attention, executive functions, and visuospatial functions are typically prominent, whereas memory impairment is more variable
Core clinical features
• Fluctuating cognition
• Recurrent well-formed visual hallucinations
• REM sleep behavior disorder, which usually precedes cognitive decline
• Parkinsonism
Supportive clinical features
• Many are described, with a new feature being hypersomnia
Indicative biomarkers
• Polysomnographic confirmation of REM sleep without atonia
• Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
• Reduced uptake of 123iodine-MIBG myocardial scintigraphy
Probable DLB—Dementia plus either
• Two or more core clinical features regardless of the presence of indicative biomarkers
• Only one core clinical feature but with one or more indicative biomarkers present
Possible DLB—Dementia plus either
• Only one core clinical feature with no indicative biomarkers present
• One or more indicative biomarkers present but there are no core clinical features

Adapted from McKeith et al. (2017) [30]

and convincing history of recurrent dream enactment behavior consistent with probable RBD was sufficient. Since the clinical diagnostic criteria were designed to be simple and practical for routine clinical use, and due to the expense and lack of availability of PSG in many clinical settings, the consensus of the authors was to consider probable RBD as sufficient. However, PSG evidence of REM sleep without atonia—along with reduced uptake on dopamine transporter SPECT or PET imaging and reduced uptake on cardiac MIBG scintigraphy—were identified as "indicative biomarkers." Other aspects of DLB phenomenology were also added or explained in more detail. For example, hypersomnia was added as a supportive feature, and the qualitative aspects of the neuropsychological profile were characterized—prominent impairment in the domains of attention/executive functioning and visuospatial functioning [30]. The key features of the updated criteria are shown in Table 6.1.

6.3 Prodromal DLB

The development of DLB surely evolves over a transitional state from normal aging to dementia in most individuals. The transitional state that is dominated by changes in cognition is known as mild cognitive impairment (MCI), and several groups have characterized MCI retrospectively and prospectively in those with clinical DLB +/− underlying Lewy body disease [41–43]. Molano et al. analyzed the clinical and

neuropsychological data on all patients who were diagnosed with MCI, prospectively followed, and eventually underwent neuropathologic examination and had limbic +/− neocortical LBD [41]. Eight subjects were identified, seven of whom developed DLB prior to death, and one died characterized as MCI. RBD preceded cognitive symptom onset in six cases by a median of 10 years. Each of the MCI subtypes was represented, with seven of the eight patients having impairment in the attention/executive functioning and/or visuospatial functioning domains. As exemplified by most of these cases, RBD was the initial clinical feature, followed by cognitive decline, then the MCI diagnosis, and subsequent development of parkinsonism, visual hallucinations, and/or fluctuations with eventual neuropathologic evidence of Lewy body disease. Another analysis showed that those patients with the nonamnestic subtype of MCI are more likely to evolve to DLB than the amnestic subtype (which is more likely to evolve to Alzheimer's disease dementia) [44].

Other prodromal DLB phenotypes would be predicted to include isolated visual hallucinations, isolated depression, pervasive apathy, and recurrent delirium. There has not been sufficient prospective data with large numbers of patients with these phenotypes to develop a clear picture of these clinical characterizations.

RBD is the disorder that precedes and continues through most of these prodromal DLB cognitive and neuropsychiatric syndromes. A schematic depiction of the RBD-MCI-DLB continuum is shown in Fig. 6.1.

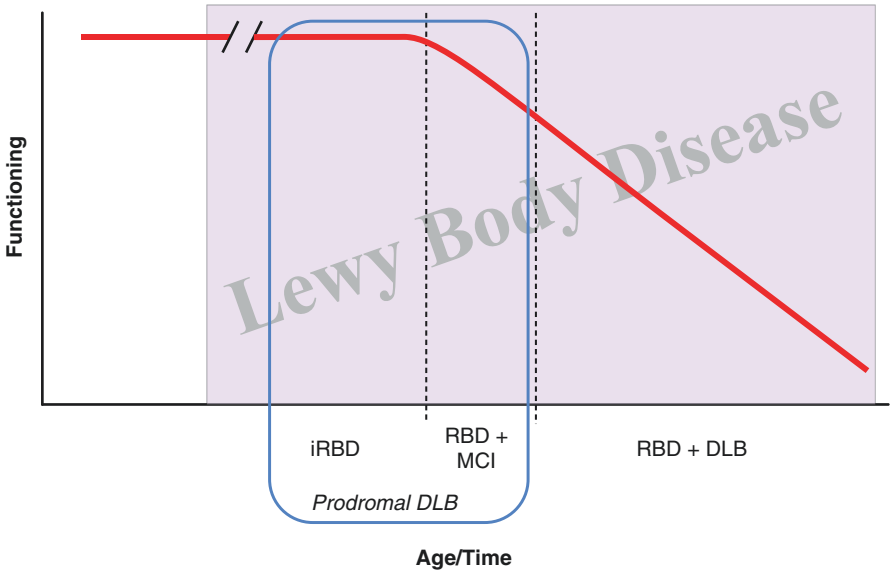

Fig. 6.1 The RBD-MCI-DLB continuum**.** This schematic representation of the RBD to MCI to DLB continuum, showing RBD followed by RBD plus MCI (with the phenotypes of idiopathic RBD and then RBD plus MCI reflecting "prodromal DLB"). Abbreviations: *RBD* REM sleep behavior disorder, *iRBD* idiopathic RBD, *MCI* mild cognitive impairment, *DLB* dementia with Lewy bodies

6.4 Analyses in Patients with Idiopathic RBD Pertinent to Dementia

There are several studies published to date which involved patients with iRBD who have been followed prospectively. The seminal paper by Schenck et al. which launched the interest in the RBD-neurodegenerative disease association showed that among 29 iRBD patients who they followed longitudinally, almost 40% developed a parkinsonian disorder at a mean interval of 3.7 years after the diagnosis of RBD and at a mean interval of 12.7 years after the onset of RBD [45]. Several have since developed cognitive impairment or dementia, with DLB features being present in most [26, 46]. Other groups of investigators have shown a similar profile of iRBD developing MCI or DLB [11, 13, 23, 33, 47–52].

Evidence of impairment on neuropsychological assessment has been documented in iRBD patients by several groups [53–55].The pattern of impairment—with deficits largely in attention, executive functioning, and visuospatial functioning and more variable performance in learning and memory—is similar to that described in MCI [56] and DLB [2, 19, 39, 44, 57].

Findings on several biomarkers in iRBD patients have also been consistent with those with DLB or PD. These include slowing on background electroencephalography [58–60], (99m)Tc-ethylene cysteinate dimer (ECD) SPECT [61], ioflupane SPECT [23, 48, 62–65], and fluorodeoxyglucose positron emission tomography (FDG-PET) [27, 66–69].

6.5 Application of the Braak Staging System for Parkinson's Disease to the Evolution of RBD to Dementia with Lewy Bodies

Braak et al. have proposed a staging system for the neuropathologic characterization of the phenotype of Parkinson's disease (PD), and this system may be applicable to the timing of the evolution of RBD in the context of evolving Lewy body disease regardless if the clinical phenotype evolves as PD or DLB [7, 11–13, 64, 70–74]. This staging system proposes a temporal sequence of α-synuclein pathology in the brain beginning mainly in the medulla (and olfactory bulb) and gradually ascending to more rostral structures [70, 71]. Dysfunction in the sublaterodorsal nucleus (SLD) +/− magnocellular reticular formation (MCRF) and associated networks (Stage 2) could lead to REM sleep without atonia (RSWA) and RBD. This temporal sequence of pathology could explain why RBD precedes parkinsonism and cognitive decline (Stages 3 and 4) and dementia (Stages 4–6) in many patients with Lewy body pathology. A schematic representation of this evolution from Stage 2 to Stages 5/6 is shown in Fig. 6.2.

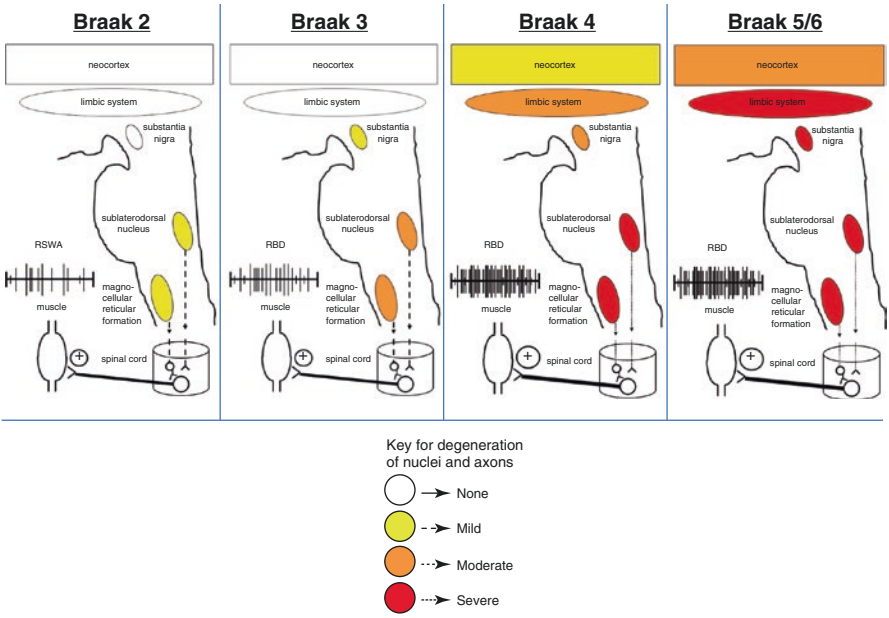

Fig. 6.2 Electrophysiologic-neurodegenerative correlations according to the Braak staging system. Schematic of the key brainstem nuclei—the sublaterodorsal nucleus and magnocellular reticular formation—and their corresponding degrees of degeneration associated with REM sleep without atonia according to Braak Stages 2–5/6. Note that overt parkinsonism and/or cognitive impairment would not be expected until at least Stage 4, but RSWA (Stage 2) and RBD (Stage 2 or 3) would occur earlier in the course. This temporal sequence of degenerative changes could explain why RBD precedes parkinsonism and dementia in many patients with Lewy body pathology. Abbreviations: *RSWA* REM sleep without atonia

6.6 The Bigger Picture in the RBD-MCI-DLB Continuum

One can then synthesize the electrophysiologic changes in REM sleep tone, the neurodegenerative changes according to the Braak staging system, and biomarker findings based on neocortical (e.g., FDG-PET) and nigral (e.g., ioflupane SPECT) integrity along this clinical RBD-MCI-DLB continuum (Fig. 6.3). This is a hypothetical model that is testable, realizing that this would require ample numbers of iRBD patients who undergo comprehensive clinical, neuropsychological, polysomnographic, and neuroimaging studies longitudinally. Yet if even some of these assumptions prove to be relatively accurate, then the ability to use biomarkers for predicting future outcomes would be enhanced. For example, those iRBD patients who demonstrate progressive but subtle changes on clinical and neuropsychological markers while also showing progressive changes in neocortical FDG metabolism

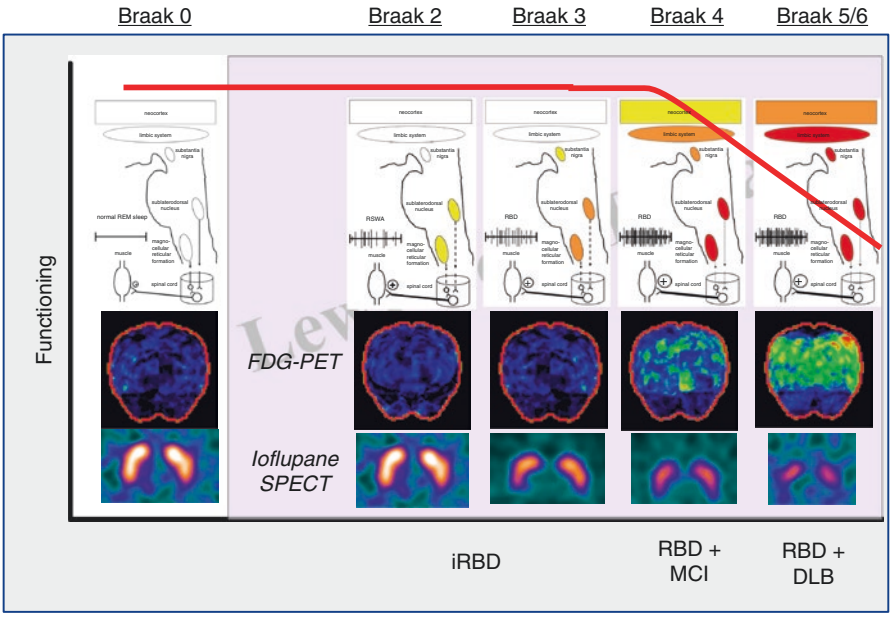

Fig. 6.3 Electrophysiologic changes in REM sleep tone, the neurodegenerative changes according to the Braak staging system, and biomarker findings based on neocortical and nigral integrity along this clinical RBD-MCI-DLB continuum. Braak Stage 0 is not associated with any clinical symptoms nor Lewy body pathology. Degenerative changes in Stage 2 would involve the sublaterodorsal nucleus and magnocellular reticular formation and potentially result in mild REM sleep without atonia but perhaps minimal if any dream enactment behavior. Overt RBD would be predicted by Stage 3, and sufficient degenerative changes may be present in the substantia nigra that could be reflected on ioflupane SPECT, but no overt parkinsonism would be evident yet. The limbic and neocortical structures are spared, and therefore FDG-PET should still show normal metabolism. Cognitive changes and associated occipital hypometabolism may be evident in Stage 4, and overt cognitive impairment plus parkinsonism would be expected in Stages 5 and 6 with corresponding changes on FDG-PET and ioflupane SPECT. Importantly, many MCI patients and a significant minority of DLB patients do not have any degree of parkinsonism early in the course, and even despite overt RBD, the findings on ioflupane SPECT may be normal. This suggests that the MCI and DLB phenotypes are associated with relative sparking of the substantia nigra in a minority of patients, and hence the classic Braak staging system may not be consistently applicable to all patients in the evolution of RBD to MCI to DLB

+/− nigrostriatal uptake on ioflupane SPECT will likely phenoconvert to MCI and subsequently DLB. Those iRBD patients who demonstrate progressive but subtle changes on clinical (especially motor measures) +/− neuropsychological markers while also showing progressive changes in nigrostriatal uptake on ioflupane SPECT but minimal to absent changes on FDG-PET will likely phenoconvert to mild parkinsonism and subsequently overt PD. And perhaps the degrees of change on many of these measures would predict the timing of phenoconversion. As explained in the figure caption for Fig. 6.3, this hypothetical model may not be applicable to all RBD

patients in the evolution to MCI and DLB due to relative sparing of the substantia nigra—at least in the early course of this evolution.

If funding is adequate to perform natural history studies with multimodal measures such as those suggested here, the scientific community will become increasingly prepared for future disease-modifying therapeutic trials to delay the onset or prevent overt DLB (or PD) in those with iRBD.

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7 RBD and Non-synuclein Neurodegenerative Disorders: A Critical Appraisal

Luigi Ferini-Strambi, Francesca Marta Casoni, and Marco Zucconi

7.1 Introduction

Numerous studies have highlighted a close association between REM behavior disorder (RBD) and synucleinopathy neurodegenerative disorders, such as Parkinson disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB).

Less commonly an association has been reported between RBD and other neurodegenerative disorders such as the tauopathies, for instance, Alzheimer disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, and pallidopontonigral degeneration. These diseases are characterized by intracellular inclusions of the protein tau in the affected neurons. It is still not clear why RBD is much less common in non-synucleinopathies, in particular whether it is due to the anatomical site of neuronal damage to specific brainstem networks involved in RBD development or to the pathology of the specific disorder.

Sporadic RBD has also been described in other neurological disorders such as Machado-Joseph disease [1–4], amyotrophic lateral sclerosis [5–9], Wilson's disease [10–14], and Huntington's disease [15, 16].

Table 7.1 illustrates the cases of RBD or patients with REM sleep without atonia (RSWA) reported in non-synucleinopathies.

A common feature of RBD in non-synuclein neurodegenerative disorders is that it rarely, if ever, precedes the clinical diagnosis of the disorder, which is a common feature in the synucleinopathies.

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Table 7.1 Number of patients with "REM Sleep Without Atonia" (RSWA) or RBD according to polysomnography in non-synuclein neurological disorders

		RSWA	RBD
Progressive supranuclear palsy	Arnulf I 2005	4/15	2/15
	Sixel-Döring F 2009	17/20	7/20
	Nomura T 2012	5/20	0/20
Guadeloupean parkinsonism	De Cock V 2007		7/9
Corticobasal degeneration	Kimura K 1997	1 (case report)	1 (case report)
	Wetter C 2002	1 (case report)	1 (case report)
	Gatto EM 2007	2 (case report)	
Alzheimer disease	Gagnon JF 2006	3/15	1/15
	Wang P 2016		5/15
Olivopontocerebellar atrophy	Quera Salva M 1986		2 (case report)
Pallidopontonigral degeneration	Boeve BF 2006		0/11
Frontotemporal dementia	Lo Coco D 2012		2 (case report)
Creutzfeldt-Jakob disease	Kang P 2016	3/14	2/14
Amyotrophic lateral sclerosis	Ebben MR		2 (case report)
	Puligheddu M 2016	10/29	0/29
	Lo Coco D 2017	4/41	2/41
Huntington's disease	Arnulf I 2008	1/25	3/25
	Piano C 2014	0/30	0/30
	Neutel D 2015	2/29	0/29
Wilson's disease	Nevsimalova S 2011	0/24	0/24
	Tribl GG 2014		4 (case report)
	Tribl GG 2016		5/35

7.2 Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), known eponymously as Steele-Richardson-Olszewski syndrome, is a rare tauopathy characterized by parkinsonism, paralysis of vertical gaze, dystonic rigidity of upper trunk, postural instability with frequent falls, frontal cognitive impairment, dysarthria, and dysphagia [17].

The first descriptions of RBD in PSP date back to the 1970s [18–21]. Since then other cases have been described, however, with a significantly lower prevalence than in synucleinopathies [6, 20, 22–24].

In 2005, Arnulf and co-workers investigated the presence of RBD in 15 patients with probable PSP, comparing their polysomnography (PSG) features with 15 PD patients and 15 controls [25]. They found a similar presence of RSWA in the two neurodegenerative disorders (27% in both PSP and PD patients) and identified two PSP patients (13%) with PSG changes compatible with RBD.

In a 2012 study of 20 patients with probable PSP compared to 20 PD patients, the changes in sleep architecture were more severe in PSP patients. The presence of RSWA was very high in both patient groups: 85% of PSP patients and 95% of PD patients. However the total amount of RSWA was lower in PSP patients (14.5 ± 17.3% of REM vs. 44.6 ± 31.3% in PD patients) [26]. RBD was found in 35% of PSP patients, regardless of the subtype of PSP.

With respect to PSP, there is agreement about the importance of the site of the lesion rather than the neuropathological mechanism (synucleinopathy vs. tauopathy) for the loss of atonia in REM sleep and the subsequent development of the RBD [25, 26].

In patients with PSP, there is loss of cholinergic neurons in the pedunculopontine tegmentum and locus coeruleus [27], which are areas responsible for REM sleep control. Damage to these areas (including the subcoeruleus) causes a progressive and direct alteration of the REM sleep executive system, leading to increased RSWA and the presence of RBD. Since neuronal loss in the locus coeruleus is reported to be more severe in patients with PD than with PSP [28], this may explain why in patients with PD the prevalence of RBD is much higher in PD.

The fact that most patients with PSP or other tauopahies develop RBD after the clinical onset of the neurodegenerative disease, compared to the synucleinopathies where RBD can predate the clinical diagnosis by months to decades, suggests that the degeneration of the pontine brainstem occurs later in the course of the non-synucleinopathies.

7.3 Alzheimer's Disease

Alzheimer disease (AD) is the most common neurodegenerative disease characterized by deposition of beta-amyloid and neurofibrillary tangles in the hippocampus and cortex and neuronal loss, resulting in cognitive and neuropsychiatric impairments.

One of the first descriptions of RBD in a patient with AD was in 1996 [29]. However subsequent anatomopathological analysis demonstrated that the patient had a Lewy body variant of AD (i.e., DLB) [30]. Another case of RBD with clinical "pure" AD has been reported, with neuropathological findings also demonstrating the Lewy body variant of AD [31].

Gagnon et al. in 2006 studied 15 patients with probable AD and compared them to 15 healthy controls [32]. AD patients had changes in sleep architecture, in particular a reduced total sleep time and a reduced number of REM sleep phases. Only one patient exhibited PSG characteristics of RBD; three other patients had RSWA. Clinically, none of these patients exhibited features of DLB, but in the absence of histopathological confirmation, it is difficult to assure diagnostic accuracy. This calls to mind the two just described cases of clinical AD with RBD that at autopsy turned out to be the Lewy body variant of AD, viz., mixed tauopathy-synucleinopathy. Perhaps there are no cases of "pure" AD with RBD.

In a questionnaire study of 218 patients with probable AD, 10% of patients reported violent nighttime behavior in combination with vivid or violent dreams. This occurred in patients with daytime hallucinations, suggesting that the presence of REM sleep abnormalities may influence the occurrence of hallucinations in AD, similar to that observed in synucleinopathies [33].

However, AD patients may exhibit various sleep disorders, including episodes of awakening during light stages of sleep, increased sleep fragmentation, obstructive sleep apnea, and "sundowning" symptoms. These can be confused with RBD

symptoms and overestimate the clinical diagnosis of RBD in the absence of PSG results [34].

In 2016, Kim and co-workers studied the different cerebral atrophic patterns in patients with PD and AD, with or without RBD, and controls using the voxel-based morphometry (VMB) [35]. In PD patients, focal cortical atrophy in the bilateral dorsolateral frontal and right-dominant frontal cortices were found in comparison to controls. AD patients showed cortical atrophy in the bilateral parietotemporal and frontal areas compared to controls. By analyzing patients with and without RBD, distinctive cortical atrophic patterns were observed in AD and PD patients with RBD. AD patients showed bilateral occipital cortical atrophic changes, whereas PD patients showed atrophy in the right inferior posterior temporal area. Based on these findings, the authors hypothesized that RBD symptoms in AD patients are correlated with atrophy in specific areas such as the temporo-occipital region. This may be due to the accumulation of cortical synuclein in AD or clinically probable AD [36, 37].

A recent review has focused on the relationship between AD and RBD [38]. The authors reviewed cross-sectional studies of RBD describing a neuropsychological profile similar to that observed in dementia related to synucleinopathies; despite this evidence longitudinal studies do not provide a conclusion about the role of neurocognitive assessment as a predictive marker in RBD. The authors concluded that the issue of differential diagnosis between AD and LBD should be further investigated according to most recent diagnostic criteria. In addition, the employment of the PSG investigation to differentiate this two types of dementia and identify the neuropathological mixed form might be crucial.

7.4 Corticobasal Degeneration and Pick's Disease

Corticobasal degeneration (CBD) is a rare, progressive neurodegenerative disease characterized by apraxia, cortical dementia, and parkinsonism with rigidity and bradykinesia. A typical sign of this disease is the "alien hand syndrome," present in approximately 60% of affected individuals. Myoclonus has also been observed in CBD. Anatomopathological studies showed a progressive and asymmetric cortical atrophy involving the anterior cerebral cortex, the frontoparietal region, the superior temporal cortex, and the basal ganglia.

The first description of RBD in a patient with corticobasal degeneration (CBD) was in 1997, involving a 72-year-old woman who was found to have RSWA and episodes of talking, singing, or various nonpurposeful movements during an all-night PSG [39].

In 2002, other authors described a 63-year-old woman with a history of difficulties in using her left arm. Neuroimaging was in accordance with the diagnosis of CBD. An initial PSG revealed only RSWA, without any movements or somniloquy. A second PSG 1 year later showed various non-violent movements of the upper limbs during REM sleep, consistent with RBD. Moreover, the second PSG showed increased chin EMG activity in 91% of the epochs compared to 64% in the first PSG, suggesting an evolving stage in the development of RBD secondary to the

neurodegenerative process involving the brainstem [40]. In 2005, Gatto et al. reported two patients with CBD patients with RSWA [41]. Using the International Classification of Sleep Disorders clinical criteria for RBD, Munhoz described RBD in only 1 patient out of 18 with CBD out of 327 patients followed at the "State of Parana Parkinson Association." The presence of RBD (5.5%) was rare in CBD compared to the presence of RBD in other disorders: 58% of PD patients, 81.9% of MSA, 74% of DLB, and 36.7% of PSP [42]. This is the largest study to date of the prevalence of RBD in CBD.

To our knowledge, no cases of RBD have been reported in patients with Pick's disease or neuronal intermediate filament inclusion disease (NIFID).

7.5 Guadeloupean Parkinsonism

Guadeloupean parkinsonism or Guadeloupean progressive supranuclear palsy (Gd-PSP) was described for the first time in 1999 [43, 44] in the Caribbean island of Guadeloupe.

Patients exhibited symptoms similar to a PSP-like syndrome, specifically levodopa-resistant parkinsonism, supranuclear oculomotor dysfunction, and instability plus severe autonomic dysfunction and visual hallucinations [45]. Histopathology is characterized by the accumulation of tau protein in the hippocampus, parahippocampal gyrus, striatum, thalamus, deep layers of the isocortex, anterior cingulum, subthalamic nucleus, mesencephalic tegmentum, locus coeruleus, transverse fibers of the pons, cerebellum, dentate nucleus, and nucleus basalis of Meynert [44]. This parkinsonism is thought to be secondary to the ingestion of a mitochondrial respiratory inhibitor contained in the fruit and infusions of leaves of *Annona muricata* (also named soursop) [45–47].

Patients with Gd-PSP have definite motor disturbances during REM sleep, with tonic motor activity and phasic movements, as well as clear behavioral abnormalities. De Cock et al. studied the PSG profile in 9 patients with Gd-PSP, 9 patients with PSP, 9 PD patients, and 9 controls. They found RBD symptoms in 78% of patients with Gd-PSP compared to 33% of PSP patients and 44% of PD patients [48]. Since the observed frequency was similar to the synucleinopathies, the authors suggested that the location of the lesion is more relevant for the genesis of RBD rather than the protein that causes the disease.

7.6 Olivopontocerebellar Atrophy

There are only two reported cases of RSWA and REM sleep behavioral disorders in this rare inherited neurodegenerative disorder characterized by progressive cerebellar dysfunction either in isolation or combined with other neurologic manifestations [49]. Nevertheless the authors did not record clinical episodes, but the PSG showed clear-cut characteristics of RSWA and increased bursts of phasic EMG activity during REM sleep.

7.7 Pallidopontonigral Degeneration

Pallidopontonigral degeneration (PPND) is an autosomal dominant neurodegenerative disease discovered in the late 1980s caused by the N279K mutation in the tau gene [50, 51]. Clinically, PPND is characterized by progressive parkinsonism with rigidity, dystonia, bradykinesia, ocular motility abnormalities, apraxia, memory dysfunction, pyramidal tract signs, perseverative vocalizations, urinary incontinence, and frontal lobe release signs. It belongs to the class of frontotemporal dementias and parkinsonism linked to chromosome 17 (FTDP-17) [52]. Interestingly, PPND is histopathologically characterized by abundant ballooned neurons in neocortical and subcortical regions and tau protein inclusions similar to those seen in sporadic CBD, but in a distribution pattern resembling sporadic PSP cases [53].

Boeve et al. described a family with PPND of whom none had either PSG or behavioral symptoms of RBD [54]. Postmortem examination of some members of the family showed alterations of the substantia nigra and the degeneration of the locus coeruleus, with almost total preservation of gigantocellular reticular formation. It was speculated by the authors that this most caudal brainstem nucleus may have a critical role in the development of RBD. However, the prevailing evidence-based literature hypothesis is that the subcoeruleus nucleus in the pons is the most implicated zone in the pathophysiology of RBD.

7.8 Frontotemporal Dementia

Frontotemporal dementia (FTD) is a common dementia characterized by relatively selective degeneration of the frontal and temporal lobes. The literature on sleep disturbances is limited because this dementia actually groups heterogeneous entities, particularly the behavioral variant FTD that was previously called the frontal variant, and the primary progressive aphasia (PPA), previously called the temporal variant.

There are only a few case reports of PSG-confirmed RBD in patients with FTD. For instance, in 2012, there was a report of a patient with RBD who a few years later began to show clinical symptoms compatible with FTD, subsequently supported by neuropsychological tests and brain imaging [55].

In a large cohort of 344 patients with RBD, two patients were found to carry the C9orf72 repeat expansion, one of the most common genetic causes in familial amyotrophic lateral sclerosis (ALS) and FTD [56, 57]. However, it is not possible to exclude the possibility of comorbid LBD, which can occur in patients with familial FTD as well as AD. There is a small subset of patients with FTD who mimic DLB, with parkinsonism, fluctuating cognition, personality and behavioral changes, hallucinations, as well as parasomnias, which could then explain the occurrence of RBD in FTD patients [58].

Conversely, in a cohort of 172 patients with RBD, no one had a diagnosis of FTD, and in no case, the presence of TDP-43, the hallmark protein of this disease, was observed [59].

7.9 Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is a prion encephalopathy characterized by rapidly progressive cognitive dysfunction, myoclonus, and an akinetic mutism state. Diffusion-weighted magnetic resonance imaging (DWI) hyperintensity and periodic sharp-wave complexes on the electroencephalogram are typical of this condition. Neuropathologic findings of CJD are characterized by spongiform changes in gray matter, gliosis-particularly hypertrophic astrocytosis-neuropil rarefaction, neuronal loss, and prion protein (PrP) deposition.

The literature on sleep symptoms in CJD consists primarily of case reports and case series.

Only a few studies have performed PSG evaluations in these patients, demonstrating in many cases the absence of REM sleep or the presence of RSWA [60]. In an observational cross-sectional cohort study of 28 patients with CJD, 14 underwent a full night PSG. Of the 8 patients who had REM sleep, 3 (38%) showed RSWA and 2 patients met the criteria for RBD [61]. The authors suggested that the presence of RBD in CJD patients may be similar to the synucleinopathy populations. It should be noted that in many patients, REM sleep was not recorded. Moreover, the small sample size does not allow to draw definitive conclusions about the prevalence of RBD in this prion disease.

7.10 Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disease characterized by rapid and progressive loss of cortical, spinal, and bulbar motor neurons, with consequent paralysis of striatal bulbar and skeletal muscles, leading to dysarthria, dysphagia, and respiratory impairment resulting in terminal respiratory failure, which is the most common cause of death [62]. Most of the cases of ALS are sporadic, but there are some familial cases (about 5–10%), with an autosomal dominant inheritance pattern due to mutations in specific genetic loci [63, 64].

The presence of RBD in ALS was first reported in 1997 [6]. Recently, 29 ALS patients were evaluated with automatic quantitative analysis of chin tone during REM sleep [8]. The average atonia index was 0.733 (normal value >0.9), suggesting a loss of the physiological atonia of REM sleep, similar to idiopathic RBD patients [65].

In particular, the lower atonia index was related to the disease severity as an extension of the neuropathological processes. The authors hypothesized that alteration of the atonia index could be secondary to a degeneration of glutamatergic neurons of the caudal pontine sublaterodorsal tegmental nucleus [66] or a lesion of the glycinergic/GABAergic premotoneurons localized in the medullary ventral gigantocellular reticular nucleus [67].

A video-PSG controlled study conducted in 41 ALS patients and 26 controls demonstrated RBD in 4.9% of subjects and RSWA in 4.9% of patients without

clinical symptoms of RBD, while no abnormalities of REM sleep was noted in healthy control subjects [9]. ALS patients with RBD showed a reduction in striatal presynaptic dopamine transporters in brain SPECT imaging.

Based on this finding, the authors suggested that RBD could be the result of the disruption of one or several key neuronal pathways in the brainstem, mainly due to an underlying degenerative process, and hence not linked only to the synucleinopathies.

It might be speculated that the presence of EMG fasciculations in ALS patients may cause difficulty with the visual scoring of EMG activity and RSWA during REM in these patients. However, the detailed scoring criteria for phasic EMG activity in REM sleep allow for excluding possible interferences of the single fiber activity in the counting of epochs of phasic EMG bursts.

7.11 Huntington's Disease

Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by behavioral and cognitive disturbances and chorea [68].

More than 80% of patients report sleep disturbances, such as insomnia, excessive movements during sleep, nocturnal awakening, and daytime sleepiness [69]. Sleep architecture is altered, with longer REM sleep latency, shortened REM sleep, excessive sleep fragmentation, reduced total sleep duration, or circadian rhythm disturbances [15, 69–72]. However, RBD is very rare in this disease. A significant correlation has been found between the disease severity and the percentage of REM sleep, but the CAG repeat length seems not to influence either REM sleep duration or REM sleep latency [73].

In 2008, Arnulf et al. studied 25 HD patients, compared to patients with narcolepsy and controls. HD patients had more frequent insomnia, lower sleep efficiency, delayed REM sleep latency, reduced REM sleep percentage, and increased periodic leg movements [15]. In two women and one man not on antidepressant drugs, video-PSG monitoring revealed complex movements and vocalization compatible with RBD. Based on this finding, the authors hypothesized that the brainstem is vulnerable to the pathological effect of the mutant protein huntingtin, which may accumulate in neurons controlling muscle atonia during REM sleep. In contrast, another study that evaluated a cohort of 30 HD patients did not show RBD or RSWA in any of the study participants [16].

In 2016, Neutel et al. evaluated 29 HD patients referred for increased nocturnal agitation [73]. The HD patients had reduced sleep efficiency and less REM sleep, but the severity of disease, as measured by CAG repeat length, did not correlate with the total sleep time, REM sleep duration, or latency to onset of REM sleep. Despite the referral for motor agitation during sleep, none of the patients showed RBD episodes during the video-PSG, and only two patients had RSWA. However, the patients had clumsy and opisthotonos-like movements during arousals from non-REM or REM sleep, of which some movements were violent and harmful. The authors concluded that the nocturnal agitation in HD seems related to anosognostic

voluntary movements on arousals, rather than to RBD. This study also indicates that the use of interview alone, without vPSG, may lead to a wrong diagnosis with overestimation of RBD.

7.12 Wilson's Disease

Wilson disease's (WD) is an autosomal recessive inherited disorder associated with deficiency of a copper-transporting ATPase resulting in pathological accumulation of copper in the brain and other organs [74]. The cerebral structures involved are the basal ganglia, but pathological changes are also observed in the caudate nucleus, internal capsule, substantia nigra, thalamus, cerebral cortex, subcortical white matter, subthalamic nucleus, cerebellum, and brainstem. Neurological symptoms include ataxia, parkinsonism, dysarthria, and dyspraxia.

Patients with WD report different sleep disturbances. RBD has been described in this disorder.

Nevsimalova et al. evaluated 24 WD patients, and they found no evidence of RBD, despite nearly half of the patients (47.3%) meeting the diagnostic cutoff ≥5 on the RBD questionnaire RBD-SQ [14].

In 2014, Tribl et al. described four WD patients with RBD, of whom three had RBD as the initial symptom of WD [10]. Transcranial sonography in all patients revealed hyperintensities of the midbrain tegmentum, an area considered crucial for the genesis of idiopathic RBD and RBD in PD [75–78]. Since WD and PD have some similar clinical features and also similar topographical distribution of basal nuclei and brainstem lesions, the authors hypothesized that the copper accumulation in these locations may be a possible causal factor for RBD [10, 79].

A recent study by the same group that analyzed vPSG data in 35 patients with WD and 41 control subjects found RBD in 5 patients, with a mean age of onset of 16 years [11]. Percentage of RSWA was significantly increased in patients compared to controls, indicating that motor system disturbances of REM sleep are frequent in WD patients and that the true prevalence of RBD in WD might even be higher. The topic of WD-RBD is further addressed in Chap. 15.

7.13 Dentatorubropallidoluysian atrophy (DRPLA)

Dentatorubropallidoluysian atrophy (DRPLA) is a neurodegenerative disease caused by an expansion of a cytosine-adenine-guanine (CAG) repeat encoding a polyglutamine tract in the atrophin-1 protein, characterized by seizure, gait disturbance, and cognitive decline. Recently RBD confirmed with PSH has been reported in a family affected by DRPLA.

In particular, two of the affected family members showed RBD before presenting other neurological symptoms. The autopsy study on the progenitor showed the presence of atrophy in the brainstem, especially in the pons, and decreased pigmentation in the substantia nigra and locus ceruleus [80].

Conclusion

Although RBD is uncommon in non-synuclein neurodegenerative disorders compared to the synucleinopathies, the occurrence in disorders where there is substantial pathology in areas known to control motor aspects of REM sleep indicates that the site of neurological damage is more important than the molecular pathology. With the exception of Wilson's disease, the consistent feature of RBD associated with non-synuclein disorders is that it occurs after clinical disease is present, rather than prior to its onset. This is in contrast to the synucleinopathies where RBD often predates clinical disease by years to decades. Tau and α-synuclein (α-syn) are abundant brain proteins with different biological functions. However, the ability of tau and α-syn to affect each other directly or indirectly has been reported, and this might contribute to the overlap in the clinical and pathological features of tauopathies and synucleinopathies [81]. On the other hand, a clear distinction between synucleinopathies and tauopathies seems to be questionable.

It should be noted that α-syn aggregates (Lewy bodies) were found in approximately 60% of familial and sporadic forms of AD, and tau aggregates (neurofibrillary tangles) were also seen in PD [82, 83]. Thus, the interactions between tauopathies, synucleinopathies, and RBD still deserve further investigation.

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RBD Associated with Paraneoplastic Neurological Syndromes and Autoimmune Disorders

8

Alex Iranzo

8.1 RBD in Paraneoplastic Neurological Syndromes

Paraneoplastic neurological syndromes (PNS) are uncommon disorders related to neoplasms outside the central nervous system, such as limbic encephalitis and subacute cerebellar syndrome [1, 2]. PNS are not caused by metastases or infiltration of a tumor in the brain. PNS are immune-mediated disorders linked to onconeuronal antibodies against neural antigens expressed by both the tumor and the nervous system. Antibodies react with an antigen located both in the tumor cells and cells of the nervous system, usually neurons and Purkinje cells. The immune system recognizes a protein expressed by the tumor as foreign and attacks this protein that is also located in the normal brain. Antibodies react with specific proteins expressed in the cytoplasm, nuclei, or surface membrane of the neuronal cells. In most PNS, the direct pathogenic role of the antibodies is debatable. Autopsy usually shows neuronal loss, gliosis, and inflammatory infiltrates of cytotoxic T lymphocytes. Interestingly, PNS may precede the diagnosis of the underlying systemic cancer. PNS are common in patients with cancers of the lung, ovary, breast, and testis and Hodgkin's disease. The clinical course is usually subacute and progressive. Symptomatology can be severe and involve any area of the nervous system. Neurological symptomatology depends on the structures where antigens are prominently expressed in the brain. Damage of dorsal root ganglia, cerebellum, amygdala, hippocampus, brain stem, hypothalamus, and thalamus is common in PNS. Neurological symptoms include a confusional state, cognitive impairment, memory loss, seizures, movement disorders, psychosis, sensory polyneuropathy, and sleep disorders.

Sleep disorders in patients with PNS have received attention only recently [3]. Prospective and well-designed studies are lacking. Only small series and case

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reports have described patients with PNS suffering from sleep disturbances. They include RBD, excessive daytime sleepiness, insomnia, and central respiratory abnormalities. In some of the reported cases with sleep disturbances, video-polysomnography (V-PSG) was not performed. In the setting of PNS, sleep disorders are not the only manifestation since they coexist with limbic syndrome, brain stem symptomatology, or hypothalamic disturbances. RBD is not the most severe neurological complaint among patients with PNS. It is possible that the presence of RBD in the setting of any PNS may have been previously overlooked because physicians frequently pay little attention to sleep and because patients and bed partners usually do not spontaneously report sleep problems. This chapter reviews the medical literature where RBD was linked to PNS.

Anti-Ma2 encephalitis. This is a PNS affecting diencephalon, limbic, and brain stem structures in any combination, and it is usually linked to lung and testicular cancers [1, 2]. There are a few reports of RBD associated with anti-Ma2 encephalitis. In these cases, RBD was apparently linked to secondary narcolepsy due to an inflammatory process involving the hypothalamus, amygdala, and brainstem. RBD, in these cases, was not the sole manifestation of the anti-Ma2 encephalitis where it is associated with coexistent cognitive impairment, gaze palsy, hypersomnia, and cataplexy. In anti-Ma2 encephalitis, RBD is usually mild and not a prominent feature of the clinical picture. There are a few case reports of patients presenting with RBD in the context of anti-Ma2 encephalitis.

A 69-year-old man with anti-Ma2 encephalitis presented with a subacute onset of severe hypersomnia, memory loss, parkinsonism, and gaze palsy. Brain magnetic resonance imaging showed bilateral damage in the dorsolateral midbrain, amygdala, and paramedian thalami. V-PSG disclosed RBD and reduced sleep efficiency of 48% and absence of sleep spindles. REM sleep was characterized by increased phasic and tonic muscular activity in the submentalis muscle and the four limbs associated with kicking and prominent limb and truncal jerking. The multiple sleep latency test (MSLT) showed a mean sleep latency of 7 min and four sleep-onset REM periods. HLA typing was negative for the DQB1*0602 and DRB1*15 alleles. CSF hypocretin level was low (49 pg/mL) [4].

A 55-year-old man presented with hypersomnolence, cataplexy, abnormal sleep behaviors, parkinsonism, and vertical supranuclear palsy. PSG showed disrupted sleep architecture and complete loss of REM sleep atonia. During REM sleep, vocalizations (talking, laughing, and singing) and arm and leg movements were observed. MSLT demonstrated reduced sleep latency of 2 min and multiple sleep-onset REM periods without muscle atonia. The patient had positive Ma1 and Ma2 antibodies, and a tonsillar squamous cell carcinoma was discovered [5].

A 63-year-old man with anti-Ma2 antibodies had diencephalic encephalitis with excessive daytime sleepiness, cataplexy, and hypocretin deficiency. PSG demonstrated fragmented and reduced sleep efficiency and sustained muscle activity in REM sleep. MSLT showed two sleep-onset REM periods and a mean sleep latency of 7 min. Neuropathology demonstrated inflammation induced by cytotoxic CD8+ T lymphocytes and complete loss of hypocretinergic neurons within the hypothalamus [6].

Limbic encephalitis associated with LGI1 antibodies (previously termed potassium channel antibody-associated limbic encephalitis) [7].

The antibodies specific for this syndrome are active against the leucine-rich glioma inactivated protein that is part of the voltage-gated potassium channel complex and is located in the surface of the neuron. This limbic encephalitis affects middle-aged or elderly individuals, mainly men, and it is not associated with gliomas. Indeed, it is usually not associated with malignancy, but in 10% of the cases, it is associated with thymomas. In this condition there is a primary insult in the mesial temporal lobe involving the hippocampus and the amygdala, with no apparent direct involvement of the brainstem. Patients present with subacute progressive cognitive impairment, confusion, disorientation in time and space, memory loss, hyponatremia, and seizures. Sleep disorders such as insomnia, excessive daytime sleepiness, and RBD have also been described in a few subjects with limbic encephalitis associated with LGI1 antibodies. The clinical syndrome is partially or totally reversible with immunotherapy. The association of RBD with this limbic encephalitis served to establish a pathophysiological link between this parasomnia and impairment of the limbic system, which could explain the intense emotions occurring in the RBD-related dreams (e.g., being attacked and chased). Other antibodies against the potassium channel complex bind the contactin-associated protein-2 (Caspr2), and the resulting neurological disorders consist of Morvan syndrome (described below), neuromyotonia (a form of peripheral nerve hyperexcitability that causes spontaneous muscular activation), and encephalitis. RBD has not yet been described in patients with Caspr2 antibodies. The identity of other potassium channel complex antibodies is unknown.

In one study of six patients with non-paraneoplastic limbic encephalitis associated with LGI1 antibodies, five had the typical clinical history of RBD in the context of encephalopathy, seizures, and excessive daytime sleepiness. V-PSG could be performed in three of these five patients and demonstrated RBD showing increased electromyographic activity in REM sleep linked to prominent limb jerking. In three patients, immunosuppression resulted in resolution of RBD in parallel with remission of the limbic syndrome and disappearance of mesial lobe hyperintensity. RBD persisted in two patients with partial resolution of the limbic syndrome [8].

In another study, 15 patients were identified with antibodies against voltage-gated potassium channels (specific LGI1 and Caspr2 antibodies were not analyzed in this study) and had limbic encephalitis ($n = 5$), Morvan syndrome ($n = 4$), and overlapping features ($n = 6$). Clinical history revealed that two patients had hypersomnia, ten had prominent insomnia, and eight had dream-enacting behaviors (four with Morvan syndrome, three with limbic encephalitis, and one with overlapping features). PSG in seven of the eight patients with dream-enacting behaviors showed normal REM sleep in one, absence of REM sleep in three, and REM sleep without atonia (but without abnormal behaviors in REM sleep) in three (one with Morvan syndrome, one with limbic encephalitis and one with overlapping clinical features) patients. NREM sleep parasomnias were not found in these patients [9].

A 62-year-old man with limbic encephalitis associated with LGI1 antibodies had RBD documented by V-PSG showing that REM sleep contained increased phasic electromyographic activity associated with multiple kicks and jerks [10].

Morvan syndrome (also known as Morvan's fibrillary chorea and Morvan's chorea). Morvan syndrome is characterized by subacute onset of severe insomnia (usually not associated with hypersomnia), disrupted sleep-wake pattern, abnormal and nearly continuous motor activation, mental confusion, daytime visual hallucinations, dysautonomia (constipation, salivation, lacrimation, urinary incontinence, hyperhidrosis, increased body temperature, tachycardia, hypertension), fasciculations, myoclonic jerks, cramps, and neuromyotonia. It is associated with Caspr-2 antibodies in the context of myasthenia gravis, malignant thymoma, or small cell lung cancer. In most cases, the syndrome responds to immunotherapy, but some cases worsen and lead to death [11].

The sleep abnormalities that characterize Morvan syndrome are insomnia and an extreme expression of status dissociatus due to breakdown of the sleep-wake boundaries [12–16]. This state is termed *agrypnia excitata* which also is present in fatal familial insomnia and alcohol withdrawal syndrome (delirium tremens) [16]. It is thought that agrypnia excitata represents a thalamo-limbic system dysfunction, although brain imaging is normal in Morvan syndrome. In agrypnia excitata, patients present with severe insomnia, generalized sympathetic dysautonomia, and nocturnal motor overactivation where subjects perform simple or complex behaviors mimicking daily-life activities such as eating, setting up a device, dressing, buttoning the pajamas, or pointing at something on the wall. This nocturnal purposeful activity is labelled *oneiric stupor* and is nearly continuous during the entire night, with quiet pauses lasting several minutes. Episodes of oneiric stupor can occur with open or closed eyes. If questioned during one of these episodes, patients may respond that they are awake, although they seem to be behaving in the context of a dream or a hallucination. The oneiric stupor episodes can emerge from any stage (relaxed wakefulness, NREM sleep, and REM sleep). In agrypnia excitata the circadian rhythmicity is lost, and motor activity is increased throughout the 24 h without any circadian pattern. Electrophysiological recordings show an extreme disorganized pattern with reduced sleep time, brief fragments of alpha-theta activity without sleep elements (probably representing wakefulness), reduction or absence of K complexes and spindles, loss or small amounts of N3 stage, and brief intrusions or clusters of REM sleep bursts without muscle atonia. Rapid shifts across subwakefulness, NREM sleep features and REM sleep without atonia are typical during 24 h recordings [12–16].

Paraneoplastic cerebellar degeneration. Paraneoplastic cerebellar degeneration is characterized by rapid progressive pancerebellar syndrome (trunk and limb ataxia, dysarthria, nystagmus) due to loss of the Purkinje cells in the cerebellum. It is mostly associated with breast and ovarian cancers, small cell lung cancer, and Hodgkin's disease. Brain neuroimaging is usually normal. Onconeuronal antibodies in paraneoplastic cerebellar degeneration are anti-Yo, anti-Ro, anti-Gad65, anti-Tr, anti-amphiphysin, anti-Hu, anti-CARP, and anti-GluR1. However, in a number of cases, antibodies are not found [1, 2].

There is a report of two patients with paraneoplastic cerebellar degeneration and RBD [17]. Two women of 43 and 66 years of age with breast cancer and paraneoplastic cerebellar degeneration (where no onconeuronal antibodies were found)

presented with PSG-confirmed RBD. It is notable that the 43-year-old woman developed symptoms of RBD for more than 2 years before the rapid onset of cerebellar symptoms, with vivid dreams and dream enactment, and her sister observed restless sleep with kicking and screaming. Immunotherapy improved RBD symptomatology in both patients, but not the cerebellar syndrome. The association of a cerebellar syndrome with RBD suggests that the cerebellum may be implicated in the pathogenesis of RBD in at least some cases. In fact, other disorders where the cerebellum is damaged, such multiple system atrophy [18] and some spinocerebellar ataxias [19], are strongly linked to RBD. Furthermore, paraneoplastic cerebellar degeneration with RBD joins Wilson's disease and the alpha-synucleinopathy neurodegenerative disorders as a neurologic disorder in which RBD in adults under the age of 50 years can precede the emergence of frank symptoms of the neurologic disorder by years, as discussed further in Chap. 15.

Anti-NMDA receptor encephalitis. Patients typically present with hallucinations, delusions, seizures, short-term memory loss, movement disorders, decreased level of consciousness, and central hypoventilation requiring mechanical support. It is usually associated with young women afflicted with ovarian teratomas. Brain magnetic resonance imaging is normal or shows abnormalities in the mesial temporal lobes, basal ganglia, and brain stem. Autopsies reveal extensive gliosis, rare T-cell infiltrates, and neuronal degeneration in the hippocampus and other regions including the brain stem. Patients can recover after tumor removal and immunotherapy [20, 21].

The most common sleep abnormality in anti-NMDA receptor encephalitis is insomnia during the acute phase, usually in combination with psychosis. It is not clear if RBD accompanies this paraneoplastic encephalitis. It has been speculated that the movement disorders seen in the anti-NMDA receptor encephalitis (complex bilateral antigravity stereotyped movements of the arms, with perioral and eye movements and less frequently involvement of the legs) represent *status dissociatus*, but this has never been proved by PSG [22]. A case report described a 58-year-old man with anti-NMDA receptor encephalitis who presented with a 4-month symptomatology somewhat resembling dementia with Lewy bodies, characterized by memory loss, aggressive behavior, visual hallucinations, and urinary incontinence. His wife reported acting out violent dreams, vocalizations, kicking, biting, and screaming during sleep occurring one or two times every night. PSG could not be performed to detect RBD or to exclude one of its mimics (e.g., confusional awakenings, severe obstructive sleep apnea) [23].

8.2 RBD in Autoimmune Disorders

Autoimmune disorders of the central nervous system are characterized by an abnormal immune-mediated response (humoral and/or cellular) against antigens expressed in the cells of the central nervous system. RBD has been described in the following autoimmune disorders: narcolepsy, multiple sclerosis, Guillain-Barré syndrome, and anti-IgLON5 disease.

Narcolepsy [24] (Chap. 11 covers the topic of narcolepsy-RBD). This disease, when linked to cataplexy and low cerebrospinal fluid levels of hypocretin, can often be associated with RBD. The severity of RBD in narcolepsy is less intense than RBD associated with the idiopathic form or secondary to a neurodegenerative disease. In very rare cases, RBD can be the first manifestation of narcolepsy, including in children. It is unknown why RBD occurs in narcolepsy, but the decreased input of hypocretinergic innervation from the hypothalamus to the limbic system and brain stem nuclei that regulate REM sleep muscle tone may play a crucial role.

Multiple sclerosis (MS). This is a common disabling neurological disease characterized by an inflammatory autoimmune demyelinating process of central nervous system. It is often seen in young people with usual onset between the ages of 20 and 45 years, with clinical relapsing-remitting and chronic progressive forms. An impressive variety of symptoms and signs (motor, sensitive, visual, dysautonomic, etc.) affecting different regions of the brain and spinal cord are characteristic. Sleep disorders can also be seen in patients with MS, particularly insomnia. Narcolepsy-like cases occur when the demyelinating plaques damage the hypothalamus. RBD has been described in a few patients with MS, particularly when the demyelinating plaque is located in the pontine tegmentum, presumably impairing the nuclei and pathways that regulate REM sleep muscle atonia.

In a study comprising 135 consecutive MS patients, the individuals were interviewed for symptoms suggestive of RBD using a semi-structured questionnaire [25]. Four of the 135 patients reported symptoms suggestive of RBD that were later reevaluated by a sleep disorder specialist. V-PSG confirmed RBD in three of these four patients, giving an estimated frequency of RBD of 1.4% in MS. None of these three patients had previously consulted their doctors because of RBD-related symptoms. Two of the three RBD patients were taking antidepressants, and RBD onset coincided with the introduction of the antidepressant drug in one of these two cases. Because the antidepressant drug in this patient could not be withdrawn due to severe depression, the cause of RBD was presumably linked to the antidepressant intake, within the context of MS. In the second patient, RBD onset was not related to a previous relapse of MS, and a second V-PSG study confirmed the presence of RBD after withdrawing the antidepressant drug for 1 month. The third patient was the only patient in whom brain magnetic resonance imaging showed a demyelinating plaque in the dorsal pons. Treatment with clonazepam at bedtime completely resolved the RBD symptoms in this third patient.

RBD can rarely occur as the presenting symptom of MS. RBD was reported as the initial manifestation in a 25-year-old woman with a 6 month history of dream-enacting behaviors. She had sudden awakenings from fearful dreams with crying, screaming, kicking, falling out of bed, and running to the door or to the window, resulting in injuries. If awakened, she always recalled a fighting dream. RBD was confirmed by V-PSG, and brain imaging disclosed multiple cerebral periventricular and pontine demyelinating plaques consistent with a diagnosis of probable MS. RBD episodes disappeared after immunotherapy, thus reinforcing how the pathogenesis of RBD was tightly linked with MS [26].

In another case report, a 51-year-old woman with MS developed acute vertigo, ataxia, diplopia, dysarthria, and bifacial weakness. Her husband described how she exhibited nightly sleep-related groaning, screaming, limb jerking and flailing, and violent thrashing. She did not recall these events or any unpleasant dreams. Brain magnetic resonance imaging showed a large confluent area of increased T2 signal in the dorsal pons. V-PSG showed excessive tonic and phasic muscle activity in the chin, arms, and legs electromyographic leads during REM sleep which was associated with vocalizations, arms and legs jerking, and flailing. Clonazepam resulted in substantial improvement in the frequency and severity of RBD symptoms [27].

Guillain-Barré syndrome. This is an acute autoimmune demyelinating polyradiculoneuritis causing peripheral paralysis. Central nervous system impairment may occur in a few cases during the acute phase of the attack consisting of psychosis and mental confusion. In one study, 13 patients with Guillain-Barré syndrome admitted in the intensive care unit were studied with a portable PSG montage including mental electromyography (but not electromyographic leads in the limbs or video recording). Patients were evaluated during the acute attack, seven had abnormal mental status and six had normal mental status. PSG recordings showed disorganized sleep pattern in the patients with abnormal mental status characterized by disorganized sleep (frequent shifts between wakefulness, NREM sleep, and REM sleep), short REM sleep latency, and REM sleep without atonia. Dream-enacting behaviors were not described. REM sleep muscle tone normalized after immunotherapy against the Guillain-Barré attack [28]. Finally, it should be noted that in the original description of RBD involving five patients, one patient had RBD emerging with the Guillain-Barré syndrome [29].

Anti-IgLON5 disease. This is a novel neurological disease initially described in 2014 in eight unrelated individuals [30]. It is characterized by a heterogeneous clinical presentation: distinct sleep pattern that includes RBD; serum and cerebrospinal fluid autoantibodies against the neuronal protein IgLON5; a strong HLA association; absence of any coexistent autoimmune disorders, neoplasms, or neurodegenerative diseases; and a neuropathological pattern characterized by tau deposits in the brain stem and hypothalamus impairing some of the nuclei that regulate sleep [30–43].

Demographic and clinical findings. The anti-IgLON5 disease occurs in adults with a similar distribution in both genders. It has not been described in children. Mean age at diagnosis is around 65 years with an age range between 45 and 83 years. Cases described were born in several countries from Europe (Spain, Austria, Germany, Italy, France, UK), Azerbaijan, Brazil, China, Australia, the Philippines, and the USA [30–43]. Clinical course at presentation is usually chronic (years) but the subacute form (months) is not rare. Median interval between symptom onset and diagnosis is 2.5 years (range, 2 months to 18 years) [39]. The onset of the symptomatology is insidious, and progression of the disease can be slow or fast. At referral, patients consult either to the general neurologist or to the sleep specialist, depending on the most predominant symptoms and severity. Reasons for referral are sleep symptoms, gait imbalance, dysphagia, and cognitive decline. At the initial visit, four distinct clinical phenotypes, according to symptom predominance, have been

identified, but overlapping features among them are the rule. The four clinical presentations are the following: (1) a sleep disorder consisting of abnormal sleep behaviors, insomnia, excessive daytime sleepiness, sleep attacks, and sleep breathing symptoms, in any combination; (2) a bulbar syndrome that may include dysphagia, dysarthria, hypersalivation, and acute respiratory insufficiency that may require intubation and tracheotomy; (3) a progressive supranuclear palsy-like syndrome with abnormal gait, falls, and gaze palsy; and (4) a Huntington disease-like syndrome with cognitive impairment and choreic movements of the limbs and face. Other signs and symptoms are a variety of oculomotor abnormalities (nystagmus, vertical and horizontal gaze paresis, abnormal saccadic pursuit eye movements), movement disorders (orolingual, foot, and brachial dystonia, mild rigid-akinetic parkinsonism), dysautonomic features (anhidrosis, hypersalivation, diarrhea, constipation, weight gain or loss, urinary urgency, orthostatic hypotension, syncope, cardiac arrhythmias, bradycardia, takotsubo cardiomyopathy, episodic perspiration), neuropsychiatric symptoms (anxiety, depression, compulsions, confusion, disorientation, delirium, hallucinations), neck pain, frontal lobe seizures, and "stiff-person"-like syndrome with cramps and limb stiffness. In the anti-IgLON5 disease, the symptoms occur with different severity and appear in different combinations and time periods of sequence.

Sleep findings. At the initial visit, about two thirds of the reported patients complain of sleep symptoms, namely, continuous excessive daytime sleepiness, sleep attacks, insomnia affecting sleep onset and sleep maintenance, witnessed apneic events, stridor, and abnormal sleep behaviors. Our impression, however, is that most, if not all, patients suffer from sleep disorders. Sleep problems can be overlooked because other symptoms are prominent and patients and bed partners do not report sleep symptoms and also because doctors did not ask about them. Direct questioning often reveals sleep problems. Most of the patients are unaware of their abnormal sleep behaviors that are only noted and reported by the bed partners. They include prominent jerks, vocalizations such as talking, and purposeful behaviors such as manipulating imaginary objects. Stridor and breathing pauses are reported only by the bed partners. Some patients may complain that they have multiple nightly episodes of enuresis. Patients with the anti-IgLON5 disease have no previous history of disorders of arousal (sleepwalking, sleep terrors, confusional arousals), RBD, or sleep-related epilepsy.

Sleep architecture shows a very complex and novel pattern that for its identification needs a full PSG with time-synchronized audiovisual recording and electromyographic leads in the four limbs (Fig. 8.1) [29]. This V-PSG pattern is characterized by (1) normal occipital alpha rhythm during wakefulness; (2) slight reduction of total sleep time and sleep efficiency; (3) a distinctive temporal sequence of sleep abnormalities, from being most abnormal at the beginning of the night to normalization at the end of the night; (4) initiation of sleep characterized by theta activity with rapid repetitive leg movements that do not fit criteria for periodic leg movements in sleep; (5) N1 sleep and N2 sleep that can be normal for some periods; (6) poorly structured stage N2 sleep characterized by spindles and K complexes with frequent vocalizations (e.g., talking, laughing, crying), simple motor activity

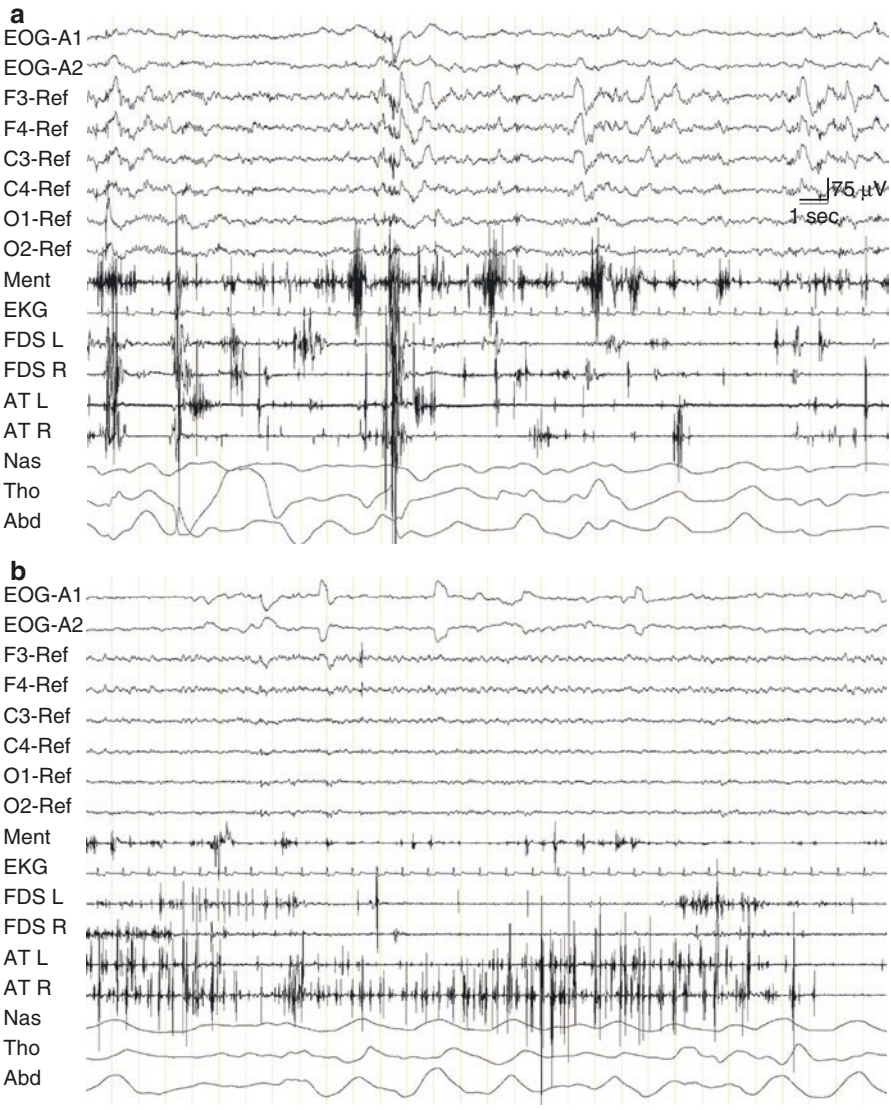

Fig. 8.1 Panel (**a**) represents a 30-s epoch of poorly structured non-REM stage 2 sleep (N2) with K complexes and spindles and increased phasic electromyographic activity in all four limbs and mentalis muscle associated with motor behaviors and vocalizations in a 53-year-old male patient with anti-IgLON5 disease. Panel (**b**) represents a 30-s epoch of REM sleep behavior disorder from the same anti-IgLON5 disease patient showing rapid eye movements, desynchronized electroencephalographic activity, and excessive phasic electromyographic activity in the mentalis muscle and the four limbs, particularly in the lower extremities. Abbreviations (from top to bottom): *EOG* electrooculogram, *F* frontal electroencephalographic lead, *C* central electroencephalographic lead, *O* occipital electroencephalographic lead, *Ment* electromyography of mentalis muscle, *EKG* electrocardiogram, *FDS* flexor digitorum superficialis muscle, *L* left, *R* right, *AT* anterior tibialis muscle, *Nas* nasal air flow, *Tho* thoracic respiratory movement, *Abd* abdominal respiratory movement

(e.g., raising the arm, punching), and purposeful behaviors (e.g., goal-directed behaviors such as sucking the thumb while apparently eating, salting food, dabbing on perfume, manipulating wires, picking up objects, knitting); (7) periods of diffuse delta activity, typical of normal N3 sleep mixed with spindles; (8) normal N3 sleep that can be seen in the second half of the night; (9) RBD; (10) obstructive sleep apnea with an apnea-hypopnea index ranging from 15 to 80/h associated with oxyhemoglobin desaturations; and (11) inspiratory stridor. Longitudinal follow-up by V-PSG has shown no dramatic deterioration of these sleep features with time, the stability of which is another feature of this unique disorder. Obstructive sleep apnea and stridor respond both to continuous positive air pressure therapy and tracheotomy. However, these treatments do not also improve the abnormal sleep electroencephalographic pattern and motor behaviors. Central apneas are much less common than obstructive apneas.

RBD can be detected in most of the patients. REM sleep is characterized by increased tonic and phasic electromyographic activity in the mentalis and excessive phasic electromyographic activity in the four limbs. The most frequent RBD manifestations are body and limb jerks. Aggressive behaviors such as punching and shouting in REM sleep occur in only a few instances. It has to be noted that the most complex sleep behaviors are seen in non-REM sleep (and not in REM sleep) and they are different from the classical NREM sleep parasomnias (sleepwalking, sleep terrors, confusional awakenings) since they are not abrupt and do not emerge from normal N3. Thus, anti-IgLON5 disease is not a typical *overlap parasomnia*, which is the topic covered in Chap. 27. However, it does comprise a unique set of combined RBD-atypical NREM sleep motor-behavioral parasomnias affecting most patients with anti-IgLON5 disease.

The sleep pattern seen in the anti-IgLON5 disease cannot be considered *status dissociatus* because (1) wakefulness can be distinguished from sleep clinically and by PSG; (2) K complexes, spindles, and delta waves are present in NREM sleep; and (3) NREM sleep can be distinguished from REM sleep. Anti-IgLON5 disease cannot be considered a form of *agrypnia excitata* because (1) there is no loss of sleep (total sleep time is mildly reduced but discernible); (2) K complexes, spindles, and delta waves and REM sleep are always present and do not decrease with the progression of the disease; (3) episodes of REM sleep are not short; (4) circadian sleep-wake pattern is normal; (5) dysautonomia is not prominent; and (6) neuropathology shows that the thalamus is not damaged.

Immunological findings. The antigen Iglon5 is a normal cell adhesion protein located on the surface of the neurons. Its function is unknown. In the anti-IgLON5 disease, autoantibodies against IgLON5 are always found in the serum and very frequently in the cerebrospinal fluid. They represent the immune hallmark of the disease. IgG4 subclass antibodies predominate over IgG1 [39]. These IgLON5 antibodies are not found in idiopathic RBD, neurological autoimmune disorders (e.g., multiple sclerosis), and neurodegenerative diseases (e.g., multiple system atrophy, Parkinson disease) [30]. Antibodies against IgLON5 have been found in one patient who fulfilled clinical diagnostic criteria for progressive supranuclear palsy but with an unusual clinical course of more than 20 years [30]. Thus, it may represent another

case of anti-IgLON5 disease. Onconeuronal antibodies (e.g., LGI1, Caspr2, Ma2, Hu, amphiphysin, NMDA, AMPA, mGLuR1, mGluR5, DPX, $GABA_B$) are absent in patients with the anti-IgLON5 disease.

The haplotypes DRB1*1001 and DQB1*0501 are detected in almost 90% of the patients tested. They are uncommon in the general population. DRB1*1001 is 36 times more frequent in patients with anti-IgLON5 disease than in the general population. The DQB1*0501 is 3.5 times more frequent in the anti-IgLON5 disease than in the general population [39].

Ancillary tests. Cerebrospinal fluid can be either normal or show mild pleocytosis and increased protein concentration. Hypocretin levels in the cerebrospinal spinal fluid are normal and oligoclonal bands are absent. Electroencephalography during wakefulness and brain magnetic resonance imaging, diffusion tensor imaging, and dopamine transporter imaging SPECT are unremarkable. Cerebral 18-FDG PET is normal or shows hypermetabolism in the basal ganglia, cortex, and cerebellum [35, 36]. Electromyography may be normal or shows multiple mononeuritis and peripheral neuropathy [40]. Neuropsychological tests may show impairment of executive function, visuospatial function, and episodic memory [32, 36]. In patients with stridor during sleep, laryngoscopy during wakefulness may be normal or shows unilateral or bilateral vocal cord abductor paresis or paralysis [30, 31].

Clinical course and therapy. The introduction of anticholinergics such as clomipramine may dramatically worsen the symptomatology. Vocal cord palsy and central hypoventilation are the causes of respiratory failure, a situation that requires intensive care support and tracheotomy. The prognosis of the disease seems to be poor in many cases. Immunotherapy (cycles of intravenous steroids, intravenous immunoglobulins, pulses of cyclophosphamide, rituximab, and plasmapheresis) is usually not helpful [30, 34, 43]. Some cases, however, have been described to improve partially after immunotherapy [36, 37, 41, 43]. Most of the patients die suddenly from wakefulness or from sleep and from aspiration pneumonia.

Neuropathology. The initial description of the disease included the postmortem examination of two patients [30]. Neuropathology showed the absence of inflammatory infiltrates and the presence of neuronal loss, moderate gliosis, and extensive deposits of abnormal hyperphosphorylated tau (with the presence of three-repeat and four-repeat tau isoforms) mainly involving the neurons of the tegmentum of the brain stem and the hypothalamus. The glia are spared. Deposits of beta-amyloid and alpha-synuclein are not seen. The nuclei damaged in the brain stem are the laterodorsal tegmental area and periaqueductal gray matter (which may explain the abnormal sleep pattern), pedunculopontine nucleus (that may cause disequilibrium with gait abnormalities and falls), and nucleus ambiguous (producing vocal cord palsy leading to stridor). The subcoeruleus nucleus is preserved. Damage of the magnocellularis nucleus in the medulla may explain the occurrence of RBD in view of the preservation of the subcoeruleus region. Other structures affected are the hippocampus, hypothalamus, and amygdala. The cortex, thalamus, substantia nigra, basal ganglia, and cerebellum are preserved or mildly affected. The anatomical distribution of this taupathy in the brain is different from the primary taupathies (e.g., Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome).

Neuropathological criteria have been established for this new entity after the postmortem study of four additional cases [38]. *Definite* diagnosis of the anti-IgLON5 disease requires detection of serum or cerebrospinal fluid IgLON5 antibodies plus neuronal loss, gliosis, and tau deposits in the neurons. *Probable* diagnosis is defined when the antibody status is unknown, but there is a compatible clinical picture, HLA DRB1*1001 and DQB1*0501, and positive neuropathology. *Possible* diagnosis is considered in cases with compatible neuropathology but without information of the clinical features and immunological status (antibodies and HLA genotype) [38]. An additional postmortem study of a single case showed brain stem and hypothalamus tau deposits in addition to microglial and neuronal TDP-43 pathology in regions without tau involvement (e.g., thalamus and basal ganglia) [40].

In the anti-IgLON5 disease, there is no evidence of malignancy. It is still unclear if we are facing a neurodegenerative and/or an autoimmune disease. On the one hand, some features suggest that the disease has an autoimmune origin (e.g., antibodies against a neuronal surface antigen, the fact that other antibodies against other members of IgLON protein family are involved in autoimmune diseases such as multiple sclerosis, and the strong HLA association). Alternatively, other findings suggest a neurodegenerative basis (e.g., no marked clinical improvement with immunosuppressive therapy, a chronic and progressive clinical course, and evidence of neuronal loss, tau deposits, and absence of inflammatory infiltrates). The anti-IgLON5 disease suggests an intriguing link between autoantibodies and abnormal deposits of tau in the brain. An experimental study with rat hippocampus showed that IgLON5 antibodies recognized the antigen on the neuron surface. Antibodies produce the internalization of the antigen, suggesting a pathogenic role of the antibodies [44]. It has been speculated that the antibodies interfere the interaction of IgLON5 with the internal cytoskeletal network, leading to abnormal tau accumulation and ultimately neuronal loss [39]. Further studies are needed to clarify the origin and pathogenesis of the disease.

Acknowledgment To Dr. Carles Gaig for reviewing the anti-IgLON5 disease section of this chapter and providing the figure.

Note Added in Proof: RBD has also been described in the setting of subjects with systemic autoimmune conditions such as Behcet's disease, Sjoegren's syndrome and rheumatoid arthritis. However, these patients also presented the cardinal symptomatology of the synucleinopathies, namely parkinsonism and cognitive impairment. (1) Fulong X, Jun Z, Waner W, Xuehua W, Wei Z, Liyue X, Fang H. A case report of REM sleep behavior disorder, Bechet's disease, Sjoegren's syndrome and cognitive dysfunction. BMC Rheumatology 2018 (in press). (2) Cosentino FII, Distefano A, Plazzi G, Schenck CH, Ferri R. A case of REM sleep behavior disorder, narcolepsy-cataplexy, parkinsonism and rheumatoid arthritis. Behavioral Neurology; 2014; 2014:572931. doi:10.1155/2014/572931.

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Lesional RBD

9

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9.1 Introduction

Long before the initial description of REM sleep behavior disorder (RBD) in 1986 by Schenck and colleagues, aggressive or violent "oneiric" behaviors suggestive of dream enactment accompanied by REM atonia loss (REM sleep without atonia, RSWA) were reported by Jouvet and Delorme from Lyon in 1965 following bilateral experimental lesioning of the peri-locus coeruleus in cats, anticipating the eventual discovery of RBD in humans [1]. Following these seminal experiments, several centers throughout Europe, Japan, and the United States reported cases of RBD-like phenomena, including two young girls with brainstem tumors associated with the development of RBD in 1975 and 1986, before RBD was formally recognized in 1986 [2–4]. Since Jouvet and Delorme's initial description of RBD-like phenomena in the cat, lesion studies in animals and RBD associated with brain lesions in humans have significantly furthered our understanding of brain networks implicated in the generation and maintenance of REM sleep atonia. The association between RBD and synuclein-mediated

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neurodegenerative diseases has become widely recognized, with most research on RBD focusing on neurodegeneration. However, the occurrence of RBD secondary to a brain lesion remains an important consideration in the differential diagnosis of abnormal nocturnal behaviors, especially in patients with a known history of autoimmune or vascular disease or those presenting with focal deficits on neurologic examination.

9.2 Diagnosis of Lesional RBD

There are currently no consensus diagnostic criteria for lesional RBD. Iranzo and Aparicio have suggested five possible criteria, including the onset and evolution of RBD associated with lesional brain pathology, that is, (1) temporally associated, (2) coincident with other lesion-associated symptoms, (3) located in a brainstem or limbic system area known to regulate REM sleep, (4) associated with remission or improvement of RBD symptoms paralleling lesion resolution, and (5) not better explained by another disorder, such as synucleinopathy, medication use, or withdrawal [5]. Brain imaging is not indicated in most newly diagnosed RBD patients, especially if they have symptoms suggestive of concurrent neurodegenerative disease. However, brain MRI should be strongly considered when RBD presents at a young age, with sudden onset of symptoms, or when accompanied by focal neurologic deficits on examination, to rule out a structural lesion as the etiology.

9.3 Demographics of Lesional RBD

To date, 31 individual cases of structural lesion-associated RBD and 13 additional cases of RBD associated with stroke from one large series have been reported in the literature (Tables 9.1, 9.2, and 9.3) [2, 3, 5–26]. Of these 44 RBD cases, 64% were men, similar to the male predominance in RBD with presumed synucleinopathy [7]. Average age of RBD diagnosis in these lesional patients was 56 (range 8–81) years, also similar to that of RBD with presumed synuclein-mediated

Table 9.1 RBD cases due to neoplasm/mass

Age/sex	Lesion location	Lesion type/neuro-diagnosis	Sleep diagnosis	Outcome	Authors
59/M	Left cerebellopontine angle	Neurinoma	RBD	Remission of RBD with tumor resection	Zambelis and Soldatos [25]
30/M	Pontomesencephalic junction at upper/mid-pons level	B-cell lymphoma	RBD	Chemotherapy improved RBD	Jianhua et al. [10]

Table 9.1 (continued)

Age/ sex	Lesion location	Lesion type/ neuro-diagnosis	Sleep diagnosis	Outcome	Authors
68/M	Left cerebellopontine angle meningioma with mass effect and upon the brainstem and compression of pons	Meningioma	RBD	No resection, RBD well-controlled with 9 mg melatonin	McCarter et al. [15]
62/M	Right petroclival meningioma with moderate-marked distortion and displacement of the pons and midbrain to the left	Meningioma	RBD	Remission of RBD with tumor resection	McCarter et al. [15]
61/F	Right cerebellopontine meningioma indenting right pontomedullary junction	Meningioma	RBD	Difficult-to-control RBD on 0.75 mg clonazepam +9 mg melatonin	McCarter et al. [15]
8/F	Pontine tumor with posterior displacement of the aqueduct of Sylvius and rhomboid fossa	No pathology available	RBD	Radiotherapy, ventriculo-atrial shunt (for increased ICP), continued DEB	De Barros-Ferreira et al. [2]
48/M	Fluid collection in operative site with flattening of left cerebellar peduncle with subtle brainstem T2 hyperintensity with flair signal change in the neighboring 4th ventricle	Posterior fossa epidermoid cyst	RBD	No follow-up	McCarter et al. [15]
28/M	Pontomesencephalic tegmentum	Following cavernoma resection	RBD + status dissociatus	RBD improved with 2 mg clonazepam	Provini et al. [18]
10/F	Right nonenhancing dorsal pontine tegmental lesion with subtle mass effect	Benign nonenhancing focal lesion of undetermined etiology	RBD	No treatment, no continued DEB	McCarter et al. [15]
10/F	Midline cerebellum	Following resection of Grade I midline cerebellar astrocytoma	RBD	No treatment	Schecnk et al. [3]

Dx diagnosis, *RBD* REM sleep behavior disorder, *DEB* dream enactment behaviors, *ICP* intracranial pressure

Table 9.2 RBD cases due to autoimmunity/inflammation/genetic causes

Age/sex	Lesion location	Lesion type/ neuro-diagnosis	Sleep diagnosis	Outcome	Authors
40/F	Right pontine tegmentum and right dorsal medulla	Inflammatory/unknown etiology	Overlap parasomnia disorder	RBD and sleepwalking improved with 9 mg melatonin	Limousin et al. [13]
30/M	Dorsomedial pontine tegmentum	Inflammatory/MS	RBD + narcolepsy	Continued RBD symptoms	Mathis et al. [14]
25/F	Pons	Inflammatory/MS	RBD	Symptoms resolved with adrenocorticotropic hormone treatment	Plazzi and Montagna [17]
51/F	Demyelinating right dorsal pontine lesion	Inflammatory/MS	RBD	RBD resolution with lesion resolution	Tippman-Peikert et al. [23]
47/M	T2 hyperintensity in right pontomedullary junction extending inferiorly to level of medulla	Central and peripheral nervous system vasculitis	RBD	No effect of immunotherapy on RBD, improvement with melatonin 6 mg and buspirone 20 mg	St. Louis et al. [21]
22/M	Pontine and mesencephalic tegmentum and mesencephalic tectum	Wilson's disease	RBD	No treatment	Tribl et al. [24]
40/F	Pontine and mesencephalic tectum	Wilson's disease	RBD + RLS + hypersomnia	No treatment	Tribl et al. [24]
69/M	Bilateral amygdala and dorsolateral midbrain	Anti-Ma2-associated encephalitis	RBD + narcolepsy	RBD not improved with IVIG and methylprednisolone	Compta et al. [28]
65/M	Bilateral mesial temporal lobes	VGKC autoantibodies	RBD	Remission of RBD with immunosuppression	Iranzo et al. [9]

53/M	FLAIR hyperintensity in left caudate, hippocampus, and parahippocampal gyrus	VGKC autoantibodies (associated with prostate adenocarcinoma)	RBD	Improvement in RBD with methylprednisolone and CellCept	McCarter et al. [15]
61/M	Bilateral T2-signal hyperintensities in the anterior medulla, middle cerebellar peduncles, dorsal pontine tegmentum, midbrain, and subcortical white matter	Autosomal dominant adult onset leukodystrophy due to lamin B1 gene duplication	RBD	Decrease in RBD with 3 mg melatonin	Flanagan et al. [8]
53/M	Hyperphosphorylated tau and neuronal loss in the pontine tegmentum, locus coeruleus, and magnocellular reticular formation (autopsy)	Antibodies against IgLON5	RBD + NREM parasomnia	No change in symptoms with immunosuppression	Sabater et al. [20]
76/F	Hyperphosphorylated tau and neuronal loss in the hypothalamus, pontine tegmentum, and medulla, most prominently in nucleus ambiguus and magnocellular nuclei (autopsy)	Antibodies against IgLON5	RBD + NREM parasomnia + stridor	Mild improvement in sleep symptoms, gait, and stridor with immunosuppression	Sabater et al. [20]

VGKC voltage-gated potassium channel, *RBD* REM sleep behavior disorder, *overlap parasomnia* RBD + NREM sleep parasomnia, *MS* multiple sclerosis, *IgLON5* IgLON5 cell adhesion molecule

Table 9.3 RBD cases secondary to infarct/abnormal vasculature

Age/ sex	Lesion location	Lesion type/ neuro-diagnosis	Sleep diagnosis	Outcome	Authors
67/M	Rostral medial pons, left of midline	Ischemic infarct	RBD + cataplexy	90% decrease in RBD and cataplexy symptoms with fluoxetine	Reynolds and Roy [19]
75/F	Left upper pons	Ischemic infarct	RBD	RBD under control with 0.25 mg clonazepam	Kimura et al. [11]
68/M	Right paramedian pons	Ischemic infarct	RBD	RBD in remission with 0.25 mg clonazepam	Zhang and Luning [26]
79/M	Bilateral cerebellar and pontine white matter lesions	Ischemic infarcts	RBD	Not reported	Peter et al. [16]
66/M	Left rostrodorsal pons	Ischemic infarct	RBD and hallucinations	RBD not responsive to 12 mg melatonin and 2 mg clonazepam	Geddes et al. [27]
81/M	Left medulla	Cavernous hemangioma	RBD	RBD decreased but persisted with clonazepam	Iranzo and Aparicio [5]
75/M	Midline pontomedullary junction	Cavernoma	RBD + OSA + RLS	"Treatment of RBD ineffective"	Felix et al. [6]
74/M	Fusiform aneurysm of proximal and mid-aspect of basilar artery with involvement of left intradural vertebral artery producing significant mass effect upon ventral and left aspect of the pons	Fusiform basilar aneurism	RBD	Improvement in RBD with 0.5 mg pramipexole	McCarter et al. [15]

RBD REM sleep behavior disorder, *OSA* obstructive sleep apnea, *RLS* restless legs syndrome

disease. However, age of RBD onset may occur at different ages depending on etiology (neoplastic/iatrogenic, 38 years; inflammatory/autoimmune/genetic, 49 years; and vascular/infarction, 70 years) [4, 24]. Isolated RBD occurred in 77% of lesional RBD cases, while 10 patients presented with RBD in association with additional sleep/wake disorders, including status dissociatus [18], peduncular hallucinosis [27], sleepwalking [13, 20], restless legs syndrome [6, 24], narcolepsy [14, 28], and cataplexy [19] (Chap. 8 covers RBD associated with paraneoplastic and autoimmune disorders).

9.4 Etiology and Location of Lesional RBD Cases

The range of etiologies in lesional RBD cases is broad, although vascular lesions account for over half of reported cases, followed by inflammatory/autoimmune lesions and neoplasm. Ischemic stroke is the most common vascular cause, with the majority of infarcts occurring in the brainstem, especially in the dorsal pons [11, 22, 26, 27]. Additionally, the volume of stroke appears to be important in the development of post-stroke RBD, with smaller infarct volume being associated with RBD [22]. This association is most likely due to the small size (and small vascular territories) of vessels supplying regions thought to control REM muscle atonia (i.e., the brainstem), whereas large vessel infarctions with large vascular territories (i.e., middle cerebral artery) are not associated with regions thought to be associated with REM sleep. Laterality may not appear to be important, since both left and right pontine strokes have been reported in RBD patients [11, 26, 27]. Vascular lesional pathology, especially brainstem cavernomas and basilar aneurysms, may also result in RBD and other sleep/wake disturbances, presumably due to distortion of the tegmentoreticular tract [5, 6, 15].

Inflammatory/demyelinating lesions causing RBD typically occur in younger individuals and may be associated with lesions outside of the pontomedullary junction. Several cases of pontine multiple sclerosis (MS) lesions have been associated with the development of RBD [14, 17, 23]. Additionally, one case of CNS vasculitis and one inflammatory lesion of unknown etiology, both in the pons, have also been reported to cause RBD [13, 21] (Fig. 9.1). Autoimmune encephalitides can also cause RBD, with or without apparent structural pathology. In the first seminal descriptive case series of IgLON5 autoimmunity (with antibodies against IgLON5 (a member of the neuronal cell adhesion molecule superfamily)) described by Sabater and colleagues, four of eight cases had RBD [20]. Of these four, one of whom also had additional NREM parasomnia, two RBD patients had pathologic evidence for diffuse neurodegeneration with structural pathology in the brainstem. In these cases, autopsy showed predominant hyperphosphorylated neuronal tau deposits and neuronal loss predominantly in the prehypothalamic, hypothalamic, and pontine tegmentum regions in the vicinity of the pedunculopontine and raphe neurons and less intensely in magnocellular nuclei of reticular formation, likely explaining REM sleep atonia loss with clinical RBD (although brain MRI was normal) [20]. Additional cases of RBD associated with IgLON5 have also been reported

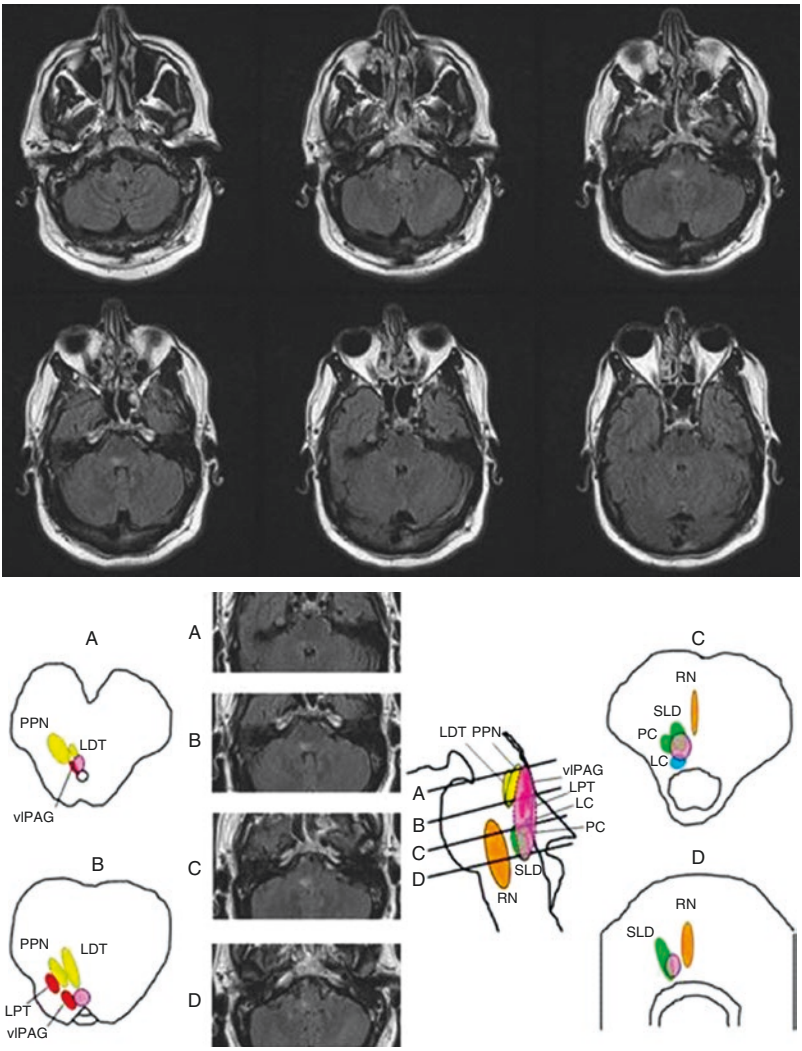

Fig. 9.1 Lesional RBD in the dorsal pontomedullary junction resulting from CNS vasculitis. **Top panel**. Coronal FLAIR intensity MRI sections at the level of the medulla and pons, showing a discrete longitudinally extensive hyperintense lesion at the level of the dorsomedial pons extending rostrally to the right superior pons ventral to the superior cerebellar peduncle. **Bottom panel**. The brainstem nuclei thought to be involved in REM sleep atonia regulation are shown on human brainstem templates. Letters for each template and corresponding MRI FLAIR image sections selected from our case represent cross-sectional views through the brainstem as shown in the midsagittal figure, with sections representing (A) the pontomesencephalic junction, (B) the upper/mid-pons, (C) the lower/mid-pons, and (D) the pontomedullary junction. The approximate location of the lesion is shown in the superimposed pink oval. *VLPAG* ventrolateral periaquaductal gray, *LC* locus coeruleus, *LDT* laterodorsal tegmental nucleus, *LPT* lateral pontine tegmentum, *PC* precoeruleus, *PPN* pedunculopontine nucleus, *REM* rapid eye movement, *RN* raphe nucleus, *SLD* sublaterodorsal nucleus, *vlPAG* ventrolateral part of the periaqueductal gray matter. As modified from Boeve BF, Silber MH, Saper C, et al. Pathophysiology of REM sleep behavior disorder and relevance to neurodegenerative disease. *Brain* 2007;130:2770–2788. Reprinted with permission from St. Louis EK, McCarter SJ, Boeve BF, Kantarci K, Rando A, Silber MH, Olson EJ, Tippmann-Peikert M, Mauerman M. REM sleep behavior disorder localizes to the dorsomedial pons. *Neurology* 2014;83(20):1871–3

by others having similar serologic evidence for autoimmunity against IgLON5 but lacking pathologic confirmation of structural neurodegenerative pathology [29, 30]. However, three cases of autoimmune encephalitis (two due to voltage-gated potassium channel (VGKC) autoantibodies, one with anti-Ma2 antibodies) have been associated with RBD in the absence of pontine lesions [9, 15, 28]. Brain MRI revealed involvement of the limbic system in all three cases, suggesting that limbic system pathology may also influence emotionally charged dream enactment and REM sleep atonia control, which is plausible given the connectivity across the amygdala, hypothalamus, and brainstem that is hypothesized to result in emotion-triggered cataplexy in patients with narcolepsy type 1 [31, 32]. However, in the context of intact hypocretinergic neurons and lesional pathology in the pons causing REM atonia loss (RSWA), this "feed forward" influence of the limbic system would cause dream enactment rather than cataplexy. Please see Chap. 8 for a more in-depth review of RBD associated with autoimmunity.

Neoplasm is the third most common cause of lesional RBD, usually presenting as a cerebellopontine angle mass. Three cases of meningioma and one of neurinoma (schwannoma, typically known as an "acoustic neuroma") at the cerebellopontine angle have been reported to cause RBD, presumably secondary to mass effect and distortion of the brainstem tegmentoreticular tract [2, 15, 25]. While the majority of neoplasms associated with RBD have been extraaxial, one intraaxial case of diffuse large B-cell lymphoma at the pontomesencephalic junction has also been reported [10]. Similar to vascular and inflammatory lesions, extraaxial cerebellopontine neoplasms with mass effect on either side of the brainstem may cause RBD.

RBD has been reported to occur rarely in association with genetic conditions. However, RBD in these cases is likely secondary to selective lesions in the pons rather than the associated genetic condition per se. RBD has been reported in two patients with Wilson's disease that had pontine/mesencephalic hyperintense brain lesions on MRI (with hypointensity of the basal ganglia on susceptibility-weighted imaging suggestive of copper deposition) [24]. Further, a patient with autosomal dominant adult onset leukodystrophy due to lamin B1 gene duplication with diffuse T2 hyperintensities longitudinally throughout the midbrain, pons, and medulla also had dream enactment behaviors [8]. Developmental malformation of the posterior fossa such as Chiari malformations may also lead to brainstem compression, thereby altering REM sleep atonia control networks that may result in RBD. In fact, one large series of patients with Chiari Type I and II malformations found that 23% of patients met polysomnographic criteria for RBD, significantly higher than would be expected in the general population (these patients were not included in the 40 cases mentioned above due to lack of reported individual patient data) [33].

Finally, iatrogenic causes of RBD may occur in patients who had instrumentation near the brainstem in the posterior fossa. While RBD can certainly occur in patients with cavernomas, RBD, along with status dissociatus, occurred following cavernoma resection at the pontomesencephalic junction [18]. Another patient developed RBD after resection of a posterior fossa epidermoid cyst with associated brainstem signal change on MRI, while a 10-year-old girl began exhibiting dream enactment behavior and REM sleep without atonia following the resection of a

midline cerebellar astrocytoma [3, 15]. Interestingly, RBD associated with neoplasm and iatrogenic causes (such as the removal of a posterior fossa mass) appears to occur relatively more frequently in children than other causes of RBD, perhaps except for narcolepsy type 1. As such, the development of RBD in a child should prompt neuroimaging of the posterior fossa. Similarly, physicians should be aware of the risk of children developing RBD following the resection of posterior fossa tumors.

9.5 Treatment and Outcomes of Lesional RBD Patients

Response to treatment of lesional RBD cases is highly variable, probably due to different etiologies and treatment responsiveness and whether the lesion resolves or persists. Interestingly, similar to synuclein-associated RBD, lesional RBD may also respond to symptomatic therapy with either melatonin or clonazepam [34]. Tumor resection and/or chemotherapy in three patients resulted in remission or significant reduction of dream enactment, whereas RBD outcomes were variable in two other patients treated with clonazepam and/or melatonin whose meningiomas were not resected [15, 25]. Similarly, in some patients with MS, RBD symptoms improved with MRI-documented lesion remission, whereas others continued to have RBD symptoms despite MS-specific therapy and despite symptomatic treatment of RBD with melatonin or clonazepam [17, 23, 35]. In both cases of VGKC autoantibody-associated RBD, dream-enacting behavior (DEB) improved with immunosuppression, whereas immunosuppression had no effect on RBD and narcolepsy symptoms in a case associated with anti-Ma2 receptor encephalitis [9, 15, 28]. Unfortunately, RBD associated with anti-IgLON5 antibodies often portends a poor prognosis and is largely unresponsive to immunosuppression, although recent evidence has also emerged of a more heterogeneous and favorable course in IgLON5 autoimmunity syndrome following immunotherapy [29]. In patients with vascular lesions, treatment response was also variable. Ultimately, we recommend initial definitive treatment of the underlying etiology causing lesional RBD when possible and feasible, as well as symptomatic pharmacologic treatment with melatonin or clonazepam to prevent injury, especially in cases where treatment for the underlying lesional cause is not possible or successful.

More than 80% of patients with presumed synuclein-mediated RBD undergo phenoconversion to a defined, clinically overt neurodegenerative disease over longitudinal follow-up [36, 37], yet thus far, available follow-up data on lesional RBD patients does not suggest that these patients develop parkinsonism, cognitive impairment, or non-motor features suggesting development of an eventual neurodegenerative disease. In the largest reported series of lesional RBD, none of the patients developed parkinsonian features or cognitive impairment suggestive of synucleinopathy over an average of 45.4 ± 35.2 months of follow-up [15]. Additionally, another patient with RBD attributed to a pontine cavernoma had a normal 123I-FP-CIT SPECT scan, which is often abnormal in presumably synuclein-mediated RBD, implicating the cavernoma as the sole culprit for that patient's dream enactment [28, 38]. Thus,

current available evidence suggests that the brain lesion causes disturbance in REM sleep atonia control that leads to clinically overt RBD symptoms. However, it remains possible that in a subset of patients with what appears to be lesional RBD, there could be interaction between brain lesions and covert underlying synuclein deposits in the brainstem, unveiling earlier clinical expression than would otherwise be seen, similar to some current hypotheses concerning antidepressant-associated RBD. Additional longitudinal follow-up outcome studies of larger series of patients with lesional RBD will be necessary to determine if there is any relationship to underlying covert synucleinopathy.

9.6 Pathophysiologic Lessons Learned from Lesional RBD

While the pathophysiology of RBD and anatomy of REM sleep control networks are discussed in great detail in other chapters of this textbook, lesional RBD has also contributed to our understanding of the control of REM sleep in humans. Evidence from studies in the cat, rat, and mouse suggest that glutamatergic neurons in the dorsal pontine sublateral dorsal nucleus (SLD), also known as subcoeruleus (SubC), located at the pontomesencephalic junction, are key in generation of REM sleep atonia [39–41] (Fig. 9.1). SLD glutamatergic neurons project to the trigeminal nucleus, ventromedial medulla, and spinal cord, synapsing on $GABA_A$, $GABA_B$, and glycinergic premotoneurons in the ventromedial medulla (gigantocellularis nucleus), resulting in hyperpolarization of trigeminal and spinal cord motoneurons and resulting in normal, physiologic REM sleep atonia [32, 39–48]. Genetic inactivation of the rat glutamate SLD leads to the development of RBD with relative preservation of daily REM sleep quantity, further suggesting that the SLD is necessary for the generation and maintenance of REM muscle atonia, but not the sleep state itself [47].

Of the 29 individually reported cases of lesional RBD, all but three cases involve lesions directly within the pontomesencephalic junction or below, or mass effect from an extraaxial lesion compressing the pons, furthering evidence for location of the SLD/SubC at the pontomesencephalic junction with descending projections through the tegmentoreticular tract to the inhibitory medullary gigantocellular nucleus [39, 44]. The three cases of RBD without brainstem lesions seen on brain imaging had limbic system involvement. While it is possible these patients had damage to the brainstem not visible with current imaging modalities, recent evidence suggests that lateral hypothalamic and forebrain structures project to the SLD and influence the onset and maintenance of REM sleep and REM sleep atonia, suggesting that patients with isolated supratentorial limbic lesions may have had RBD evolve due to disruption of this circuit [40].

Interestingly, intraaxial lesions are more likely to cause RBD as well as other symptoms (such as narcolepsy, cataplexy, status dissociatus, sleepwalking, and peduncular hallucinosis), while extraaxial lesions appear to cause DEB alone. Extraaxial lesions likely displace longitudinal tracts such as the tegmentoreticular or reticulospinal tracts distal to the SLD, causing incomplete REM sleep muscle atonia,

whereas intraaxial brainstem lesions may damage nuclei directly or damage structures superior to the SLD involved in the generation of REM sleep, leading to several sleep/wake abnormalities other than RBD [44, 47]. Of reported lesional RBD cases, the majority are not bilateral, with lesions on either side of the brainstem leading to RBD, suggesting that a unilateral lesion is sufficient to cause RSWA and RBD symptoms, similar to a previous lesional study showing that unilateral ventral mesopontine junction lesions were sufficient to cause RSWA in cats [12, 49]. Given the diversity of causative pathologies seen in lesional RBD cases, and recent evidence of genetic inactivation of the glutamate SLD leading to RBD symptoms, location of the lesion and not the underlying disease process (i.e., inflammatory/demyelinative, infarct, vascular malformation, tumor, surgery, etc.) appears to be the principle factor related to the development of RBD [47]. However, some patients have complete remission of RBD symptoms with radiographic remission of lesions (i.e., as in MS) [23], while other patients continue to have RBD symptoms despite radiographic remission (i.e., a case of vasculitis) [21]. Mechanistic difference between disease processes may result in transient or permanent damage, and varying degrees of damage may impact nuclei directly, projections within the REM atonia control network, or both, leading to variable influences on persistence or resolution of RBD symptoms irrespective of grossly visible lesion persistence on neuroimaging.

Conclusions

Lesional RBD typically occurs following insult to the brainstem, especially when involving the dorsal pons or projections of the dorsal pontine sublateral dorsal nucleus and/or medullary nucleus magnocellularis, supporting growing evidence for pontine governance of REM sleep atonia. A variety of pathological processes have been implicated in lesional RBD, suggesting that lesion location rather than etiology is the primary determining factor in the development of RBD. Lesional RBD typically evolves acutely or subacutely, with or without additional accompanying focal neurological symptoms and signs suggestive of brainstem dysfunction, but in the case of a slowly growing tumor (e.g., a cerebellopontine angle mass, such as an acoustic neuroma), RBD can evolve more indolently and chronically, so a careful neurological history and examination need to be performed in all patients with RBD. In patients with abrupt onset of focal neurological symptoms and associated DEB, especially in children, a brainstem lesion or limbic encephalitis must be considered with prompt brain MRI to exclude lesional pathology, as treatment of the underlying condition, such as resection of a tumor, or immunotherapy to decrease inflammation, may improve or resolve DEB and potentially prevent other neurological complications associated with a structural brain lesion. Patients who suffer brainstem injury through infarct or inflammatory processes should also be queried about possible dream enactment and followed carefully for possible development of RBD so that timely therapy may be initiated to prevent injury.

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RBD, Antidepressant Medications, and Psychiatric Disorders

10

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10.1 Introduction

The recognition of REM sleep behavior disorder (RBD) as a novel distinct type of parasomnia in 1986 was a landmark discovery in sleep medicine. RBD is not only notorious for the resulting sleep-related injuries and violence but also for its heightened risk of neurodegeneration. Longitudinal studies have found that RBD has shown a very high specificity of predicting synucleinopathy, including Parkinson's disease (PD), multiple system atrophy (MSA), and dementia of Lewy bodies (DLB). While various case cohorts across the world initially reported a homogeneous demography of typical idiopathic RBD (iRBD) that is typically diagnosed in elderly men during their early 60s, a few "variants" of RBD have been increasingly reported. These include early-onset RBD, RBD in women, RBD in patients with narcolepsy, and RBD with psychiatric illnesses, including those taking psychotropic medications, especially antidepressants. These clinical variants differ from the typical iRBD profile in terms of demographic characteristics and clinical correlates: onset

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at a younger age, a higher proportion of females, and a relative absence of prodromal markers for neurodegeneration. (Chapters 15 and 16 cover the topics of RBD in younger adults and gender issues; Chapter 11 covers the topic of RBD in narcolepsy, including the triggering or aggravating of RBD by antidepressant therapy of cataplexy and/or co-morbid depression or anxiety.) In particular, there is ongoing controversy over whether the RBD features presented in the patients with an earlier onset are solely related to the effects of either antidepressants or mental illness per se or to the results of a combination of both and/or other factors. In this chapter, we will review the available evidence on RBD in the context of mental illnesses and antidepressants.

10.2 Epidemiology of Co-morbid RBD and Psychiatric Illnesses

10.2.1 Prevalence of Psychiatric Illnesses in iRBD

In a number of case series of typical iRBD, the prevalence of psychiatric illnesses ranged from 9 to 33% [1–4]. The majority of the psychiatric diagnoses included depression, followed by anxiety disorders. Ostensibly, the usage of antidepressants in typical iRBD cases had also been prevalent [5]. In a multicenter international case-control study, the associations of typical iRBD with depression and use of antidepressants had been further confirmed [6]. With 300 pairs of RBD controls, this study reported that patients with iRBD had a twofold increased risk of having depression and the odds ratio (OR) of antidepressant usage and lifetime exposure to antidepressants was 2.2 and 1.9, respectively. Among various types of antidepressants, selective serotonin reuptake inhibitor (SSRI) was found to be associated with an OR of 3.6, while other types of antidepressants were not found to show any significant association. In other words, there is a higher prevalence of depression and antidepressant usage, particularly SSRI, among patients with typical iRBD. However, when comparing iRBD patients of early-onset (<50 years old) with the late-onset (>50 years old) ones, the former had a higher percentage of antidepressant usage; co-morbidities with other disorders, such as narcolepsy and depression; female predominance; and a lower percentage of neurodegenerative diseases [4, 7–9].

10.2.2 Prevalence of RBD Among Patients with Psychiatric Illnesses

Although the close association of RBD with antidepressants and psychiatric illnesses was evident in sleep centers, this observation might potentially represent referral and selection biases. Thus, it is imperative to investigate the presence of

RBD features among patients in psychiatric clinics. Over the past decades, there have been sporadic case reports and case series of RBD found in psychiatric patients (pRBD), but the clinical epidemiological data remain very limited. The first systematic epidemiological study on pRBD was conducted in an outpatient psychiatric clinic with over 1200 patients diagnosed with a variety of psychiatric illnesses [10]. This study had a three-phase design; the first phase involved screening all the recruited patients with a core question: "Have you ever suffered from sleep-related injury?," followed by a clinical interview for the ascertainment of sleep diagnosis with those screened either positive or negative for RBD, and then the video-polysomnographic assessment in the selected patients with active symptoms. The study reported that the lifetime and 1-year prevalence of RBD symptoms was 5.8% and 3.8%, respectively. The prevalence of RBD in the psychiatric populations was much higher than that of iRBD (0.38%) reported in the community-based elderly population. Among various psychiatric diagnoses, RBD was found to be more common among those of depressive disorders, including depression and dysthymia [10]. Those with RBD symptoms also had a higher prevalence of other REM-related sleep problems, such as nightmares and sleep paralysis.

10.2.3 Comparison Between iRBD and pRBD

Are there any differences or similarities in the presentation of RBD among the pRBD patients followed up in the psychiatric clinic and those typical iRBD cases seen in a sleep clinic? A comparative study reported that these two groups have similar clinical presentations and symptom severity [11], as measured by the REM sleep behavior disorder questionnaire-Hong Kong (RBDQ-HK) [12]. Both groups reported bad dreams or nightmares with common themes and intensifying feelings of agitation, anger, and fear. In addition, both groups showed similar nocturnal behavioral manifestations, such as sleep-talking, shouting, and dream-enacting behaviors, and had a high degree of sleep-related injury (SRI) (over 50%). However, pRBD reported more dreams with feelings of sadness and more subjective disturbances from their sleep problems, while those typical iRBD cases had a higher prevalence of behavioral consequence of RBD of falling out of bed [11]. Table 10.1 summarizes the comparison of demographic and clinical characteristics between iRBD and pRBD.

Table 10.1 Comparison of the demographic and clinical features between typical iRBD and pRBD

	Typical iRBD [1–3, 11, 36]	pRBD [11]
Age at diagnosis	60s	40–50s
Gender (male/female)	4:1	2:3
History of sleep-related injury	59–80%	52%
Conversion to synucleinopathy	Up to 80%	Unknown

iRBD idiopathic RBD, *pRBD* RBD co-morbid with psychiatric illnesses

10.3 Dream-Enacting Behavior in PTSD: A Different Form of Parasomnia from RBD?

Dream-enacting behaviors have often been reported in patients diagnosed with post-traumatic stress disorder (PTSD) [13–19]. In a recent case series of four PTSD patients, the authors proposed this type of parasomnia as a separate entity and named it as "trauma-associated sleep disorder" (TSD) [13]. TSD was suggested to be different from RBD with the following features: a close relationship with traumatic experiences, common occurrence in younger males, and the nightmare theme replaying the past traumatic experiences. The nocturnal behaviors in TSD ranged from thrashing movements to more complex dream enactment behaviors, which might occur in both REM and NREM sleep. However, these cases also displayed PSG features of loss of REM muscle atonia, with REM-related muscle activities of 15–38%, and dream-enacting behaviors that were compatible with those of typical RBD. These features apparently also fulfilled the diagnostic criteria of RBD in the latest International Classification of Sleep Disorders (ICSD) 3rd edition. In terms of the treatment strategies for TSD, it was suggested that clonazepam was largely ineffective, while prazosin and imagery rehearsal therapy, which have been well-recognized as the treatments for PTSD-related nightmares, were found to be effective. Nonetheless, there was no well-documented clinical trial of clonazepam or a comparison of the treatment efficacy between prazosin and clonazepam for TSD. More clinical and longitudinal data would be needed to support TSD as an independent clinical entity that is different from other parasomnias. Nonetheless, instead of considering this condition as a separate, unique disease entity at this juncture, examining the RBD manifestations in psychiatric patients may provide an opportunity to unfold the pathophysiology of RBD, particularly the REM sleep atonia control and the effect of nightmares in RBD. The successful symptomatic control with prazosin and imagery rehearsal therapy targeting recurrent nightmares in the first small case series of TSD might also shed light on the mechanism and potential alternative treatment options for RBD.

10.4 Etiologies Linking Up Depression, Antidepressants, and RBD

10.4.1 Antidepressants and RBD: Is It Merely a Drug-Related Effect?

The first case report of drug-induced RBD features was published in 1970 by Akindele et al. on phenelzine, a monoamine oxidase inhibitor [20]. A review paper on drug-induced RBD concluded that several drugs might be able to induce RBD symptoms, including various types of antidepressants, acetylcholinesterase inhibitor, and β-adrenoreceptor antagonists [21]. Most commonly reported drugs associated with RBD were antidepressants, including tricyclics,

SSRI, monoamine oxidase inhibitor (MOI), noradrenergic and serotonin reuptake inhibitor (NaSRI), and serotonin-norepinephrine reuptake inhibitor (SNRI). These cases often had underlying psychiatric illnesses or co-morbid conditions that might additionally predispose them to developing RBD, such as narcolepsy and PD [22–26].

One of the possible explanations for drug-induced RBD, especially antidepressants, is the impact on REM muscle tone, REM sleep without atonia (RSWA), which is a pathognomonic sign of RBD [27]. An open-label study of 31 depressed patients without RBD symptoms found that the administration of a SSRI (sertraline) resulted in an increase in phasic and tonic EMG activities during REM sleep and the effect plateaued out after 2 weeks of treatment [28]. In addition, previous studies found a higher degree of phasic activity of the anterior tibialis rather than submentalis muscles among individuals taking antidepressants [28, 29]. Taken together, there is some evidence to support that antidepressants may potentially precipitate RBD by inducing RSWA.

In order to understand the intriguing relationship between antidepressants and RBD, a few studies compared the RSWA features across typical iRBD, pRBD, and non-RBD depressed patients (with or without antidepressant treatment) [11, 29, 30]. These studies found a significant gradient of RSWA across typical iRBD, pRBD, and the non-RBD depressed subjects who were taking a similar regime of antidepressants. Consistent results have also been reported in patients with RBD symptoms (typical iRBD and pRBD) who had a much higher degree of RSWA than those non-symptomatic ones (i.e., non-RBD depressed subjects taking antidepressants or drug-naïve depression without RBD symptoms). Another important finding is that pRBD, but not non-RBD depressed subjects who were taking antidepressants, displayed tonic EMG activities in REM sleep, which were considered as a hallmark sign of RBD [11, 29]. This finding suggested that although antidepressants could induce RSWA, the development of RBD symptoms is likely more than a simple, direct effect from antidepressants. This is in line with the clinical observation that the risk of having RBD symptoms was 1 out of 20 (5%) among those taking antidepressants [10].

A retrospective review of PSG recordings of over 1400 participants taking antidepressants including SSRIs and SNRIs found that only 12.2% ($N = 176$) had RSWA. In addition, the presence of RSWA was not found to be associated with age, gender, OSA, and the types of antidepressants (e.g., tricyclics, SSRIs, NaSRI, or SNRIs) [30]. Among those 176 participants with RSWA, only 7 of them (~4%) showed RBD clinical symptoms. The possibility of RBD being more than a drug-induced condition may be further supported by the variable clinical outcomes and polysomnographic findings upon the cessation of psychotropic medications. Some case reports documented a full resolution of RBD symptoms upon the cessation of medications [23, 24], whereas others had persisted symptoms or required additional drug treatment, such as clonazepam, to manage the RBD symptoms [24–26]. And one study reported a restoration of REM sleep atonia upon the withdrawal of the antidepressants [20], while others reported a persistence of REM muscle abnormalities [24, 26].

10.4.2 The Role of Psychiatric Illnesses Per Se in Precipitating RBD

Given the vivid, aggressive dreams and dramatic features of the dream-enacting behaviors, RBD may be conceptualized as a "REM-related motor disorder" and a "dream-related disorder." Hence, it would be important to examine if psychiatric illnesses could give rise to these two components.

In iRBD, the tendency to having aggressive and violent dream content is well-documented but poorly understood. The nightmares and violent dreams could serve as a supratentorial drive to kick off RBD symptoms in vulnerable individuals. In mental illnesses, such as PTSD and depression, a common feature is the high prevalence of nightmares. Compared to non-RBD depressed subjects, patients with pRBD had a higher prevalence of nightmares [10, 11]. Although the content of nightmares in PTSD (trauma related) may be different from that of depression, the dreams associated with these two conditions are characterized by strong emotions (often negative), which could serve as a drive for dream enactment in those vulnerable individuals. In addition, the use of antidepressants may induce nightmares with intense dream recall.

The next question is whether there is any intrinsic pathophysiology affecting REM muscle atonia in drug-naïve patients with psychiatric illnesses, such as depression. A recent study reported that patients with drug-naïve depression displayed tonic and phasic REM muscle activation [28], which supports the assumption that REM sleep atonia control is disrupted in patients with depression. REM sleep atonia is thought to be controlled by motor neuron inhibition by glycine and GABA and the cessation or reduction of multiple excitatory cell systems, such as glutamatergic, noradrenergic (NA), serotonergic, dopaminergic, and hypocretinergic activity during REM sleep [31]. These excitatory neurotransmitters contribute not only to REM sleep muscle control but also mood state. Among all the possibilities, NA is one of the potential pathways linking up psychiatric illnesses (including depression, PTSD) and RBD. In PTSD and depression, a significant decrease in the number of neurons in locus coeruleus (LC) has been demonstrated [32–34]. Some other studies did not find any changes in LC cell number in depression but noted that there were changes in NA function. Hence, it is suggested that there is a complex dysregulation in the LC-NA system in depression [35] and hence a disruption of the normal REM inhibition of muscle activity resulting in RSWA.

10.4.3 Possibility of Dopamine Dysfunction and Neurodegeneration in Patients with Co-morbid RBD and Depression

While iRBD has been found to be associated with synucleinopathy and dopamine dysfunction, a recent neuroimaging study also reported dopamine dysfunction in pRBD [36]. This study consisted of 29 subjects, including pRBD, depressed control subjects, and healthy controls, with a relatively younger age (mean age = 47 years).

The study reported that all subjects had normal dopamine function in reference to the threshold to diagnose PD. However, patients with pRBD had significantly lower presynaptic dopamine function when compared with the other two groups. The 18F-DOPA uptake was found to be inversely correlated with the severity of RBD symptoms and the degree of RSWA. This study also reported that pRBD subjects were more likely to show olfactory dysfunction compared to the controls. Although all the depressed subjects in this study were taking antidepressants and the drug effect could not be completely eliminated, this study provided the first piece of evidence that pRBD is associated with a lower level of dopamine neurotransmission. While dopamine dysfunction is a core pathophysiological finding in RBD and synucleinopathy, there is a debate about the direct causative role of dopamine dysfunction in RBD. In the Braak staging system [37], RBD is regarded to be associated with stage 2, and neuronal damage would begin in the lower brainstem before progressing rostrally to affect the nigral circuits where the degeneration would result in Parkinsonism features. However, early involvement of NA and cholinergic pathways has also been found in RBD, which could result in dopamine dysfunction and RSWA [31, 38]. Further study will be needed for the understanding of underlying neural circuitry and neurotransmitter disturbances in pRBD.

While typical iRBD has a high specificity in predicting PD, it remains unclear whether patients with co-morbid RBD and depression are also at a higher risk of developing neurodegeneration. There is some evidence from a RBD cohort study to suggest that a lifetime diagnosis of depression is associated with the conversion to Parkinson's disease in iRBD, with a hazard ratio of 6.8 [39]. On the other hand, another 10-year prospective cohort study did not find a significant association [40]. A cohort study on iRBD has shown that those taking antidepressants seemed to have a lower risk of developing neurodegenerative disease. The study, however, also found that iRBD patients taking antidepressants were associated with significant abnormalities of several neurodegenerative markers, such as olfaction, color vision, constipation, systolic blood pressure drop, and motor symptoms as assessed by Unified Parkinson Disease Rating Scale (UPDRS) [41]. These abnormalities were indistinguishable from those of iRBD who were not on antidepressants. These findings suggested that an underlying neurodegenerative process is also evident among those iRBD taking antidepressants. Specifically, the use of antidepressants in these depressed patients (with presumed underlying neurodegeneration) accelerated the emergence of RBD without accelerating the emergence of frank neurodegeneration during the follow-up period of that study [41]. Further research is needed to determine whether antidepressants have a protective role in lowering or aggravating role in increasing the risk of development of neurodegenerative diseases in iRBD.

Although neurodegeneration as the underlying pathophysiological basis in pRBD has not been well established, there are emerging data in this aspect. In 2005, a case report from the UK reported a 64-year-old man presenting with RBD and Parkinsonism features, with a background of depression since the age of 42 [42]. A case-control study also reported that pRBD subjects were more likely to show olfactory dysfunction, which is regarded as one of the early neurodegenerative markers in synucleinopathy [36].

Table 10.2 Possible etiologies of pRBD

1.	Antidepressant effect • Inducing REM sleep without atonia • Nightmares
2.	Mental illnesses • Neurotransmitters, e.g., noradrenaline, dopamine • Intense dreams and nightmares
3.	Underlying neurodegeneration

While depression and iRBD are both regarded as early manifestations and non-motor symptoms of PD, the clinical significance of co-morbidity between depression and RBD on neurodegeneration needs to be further investigated with prospective data. Distinct hypotheses can be generated that either the presence of depression and RBD might accelerate the neurodegenerative process or more likely that an underlying neurodegenerative process manifests as early depression and RBD features in a certain subgroup of patients with depression [36]. The identification of this very early prodromal neurodegenerative phase may serve as an important clinical phase to understand the progression of depression and RBD to PD and may provide a potential window for early neuroprotective therapeutic intervention [36]. Hence, further clinical and neuroimaging follow-up of this group of patients is warranted to determine the timeline of any emergence of neurodegenerative features over time (Table 10.2).

10.5 Management

While more research is needed to further understand the co-morbidities of RBD and psychiatric illness, clinicians should be on the alert to look for RBD in psychiatric patients, given their common occurrence, potential risk of sleep-related injury, and associations with more severe mood symptoms. In daily clinical practice, a thorough review of any psychiatric history, sleep history, and medication use is warranted for these patients. As clinical and video-polysomnographic features are both needed for determining the diagnosis of RBD, a referral to sleep specialists is highly recommended. The video-polysomnographic assessment not only documents the RBD features, including the quantification of the RWSA and the detection of abnormal REM sleep behaviors, but also allows clinicians to explore/rule out the presence of other sleep disorders that could potentially precipitate or mimic RBD symptoms, such as severe obstructive sleep apnea syndrome (OSAS) [43].

There is no clinical guideline in the management of RBD in patients with psychiatric illnesses at this moment. However, with reference to the treatment guideline for typical RBD [44] and the available literature, some recommendations are summarized as follows:

1. Ensuring home safety

   Home safety is regarded as the first recommended treatment in the practice guidelines of RBD [44]. Similar to typical RBD, sleep-related injury (SRI) and

violence are serious consequences in patients with pRBD as a result of dream enactment behaviors. The prevalence of SRI goes up to 52% in pRBD [11]. Different types of injuries, such as bruises, lacerations, sprains, and fractures, and even violent acts, such as attempting to strangulate bed partners, have been reported [10]. Hence, the implementation of home safety measures for patients and their bed partners is of utmost importance. Modifications of the sleep environment, such as putting cushions and mats around the bed, placing the mattress on the floor, and removing potential dangerous (sharp) objects from the bedside, are highly recommended. Management education provided to bed partners on how to handle patients during their dream enactment episodes is also important [45].

2. Optimizing treatment of the psychiatric co-morbidities

   Given that stress and psychopathology could potentially precipitate RBD in vulnerable individuals, timely management of the psychiatric illnesses by both pharmacological and non-pharmacological approaches is suggested. The initiation of drug treatment with antidepressants should not be hindered if clinically indicated, and a thorough discussion and careful observation of the nocturnal symptoms should be highlighted throughout the treatment period.

3. Considerations of drug treatment

   Drug treatment and dosage modification should be considered in patients with co-morbid RBD and psychiatric illnesses. Although antidepressant use may not be the sole contributing factor of RBD, its use should be regularly reviewed, particularly among those reporting a close temporal association of the initiation of antidepressants with the onset of RBD symptoms. There have been a few case series reporting the resolution of clinical RBD symptoms upon withdrawal of the psychotropic medications. The cessation of antidepressants should be weighed against the need of treatment of concurrent psychiatric illnesses. Various classes of antidepressants, except bupropion (a dopamine noradrenergic reuptake inhibitor), have been reported to be associated with RBD. Hence, it would be worth trying to switch to bupropion for those individuals who are suspected of having drug-induced RBD. Its use as an alternative antidepressant in pRBD should be judged on an individual basis, with the consideration of the side effect profile.

   The efficacy of clonazepam and melatonin, which are regarded as the co-first-line treatments for typical RBD [42], has not been well studied in pRBD. pRBD patients usually are of younger age; however, they could still be susceptible to various side effects including sedation and fall risk, as they are likely to be taking concomitant medications for their psychiatric illnesses. Among patients with PTSD, prazosin and imagery rehearsal therapy have been suggested to be effective remedies for ameliorating nightmares and RBD [13].

4. Monitoring symptoms and neurocognitive assessment

   Although the risk of developing a neurodegenerative disorder has not yet been well demonstrated in pRBD patients, regularly monitoring and evaluation of the RBD symptoms, longitudinal assessment of the neurocognitive profile, and a search for other neurodegenerative markers are needed.

Note Added in Proof: The following are five recent pertinent publications: (1) Okuda M, Iwamoto K, Miyata S, Torii Y, Iritani S, Ozaki N. Early diagnosis of Lewy body disease in patients with late-onset psychiatric disorders using clinical history of REM sleep behavior disorder and 123 I-MIBG cardiac scintigraphy. Psychiatry Clin Neurosci 2018; doi: 10.1111/pcn.12651. (2) Fujishiro H, Okuda M, Iwamoto K, et al. REM sleep without atonia in middle-aged and older psychiatric patients and Lewy body disease: a case series. Int J Geriatr Psychiatry 2017;32:397–406. (3) Tan L, Zhou J, Yang L, Ren R, Zhang Y, Li T, Tang X. Duloxetine-induced rapid eye movement sleep behavior disorder: a case report. BMC Psychiatry 2017;17:372; doi: 10.1186/s12888-017-1535-4. (4) Ryan Williams R, Sandigo G. Venlafaxine-induced REM sleep behavioral disorder presenting as two fractures. Trauma Case Rep 2017;11:18–19. (5) Lee HG, Choi JW, Lee YJ, Jeong DU. Depressed REM sleep behavior disorder patients are less likely to recall enacted dreams than non-depressed ones. Psychiatry Investig 2016;13(2):227–31.

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REM Sleep Behavior Disorder in Narcolepsy

11

Giuseppe Plazzi

11.1 Introduction

Narcolepsy is a rare and lifelong central nervous system disorder of hypersomnolence that mainly arises in childhood and in early adulthood [1, 2] and that greatly impacts on quality of life, independently from culture and geographic provenance [3]. Since its identification, excessive daytime sleepiness with sleep attacks and cataplexy are the core symptoms of narcolepsy [4, 5]. The neurophysiological fingerprint of sleep episodes is the rapid eye movement (REM) sleep intrusion at sleep onset or into wakefulness.

According to the current *International Classification of Sleep Disorders, Third Edition* (ICSD-3) [6], the clinical manifestations also include dissociated REM sleep phenomena such as sleep paralysis and hypnagogic and hypnopompic hallucinations and disrupted nocturnal sleep with frequent awakenings [7]. The ICSD-3 subdivides narcolepsy into Type 1 narcolepsy (NT1), characterized by cataplexy and a low level of cerebrospinal hypocretin-1 (CSF hcrt-1), and Type 2 narcolepsy with normal CSF hcrt-1 level and without cataplexy [6]. An autoimmune process resulting in the loss of dorsolateral hypothalamic hypocretin (orexin)-producing neurons, trigged by environmental factors, is the main pathogenic hypothesis, which receives support from the strong association of NT1 with the human leukocyte antigen (HLA) DQB1*0602 allele and other genetic variants of genes involved in the immune response (such as the T-cell receptor alpha) and further supported by the clinical evidence of environmental triggering factors such as streptococcal infections close to disease onset and by the increased

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incidence of narcolepsy following the Pandemrix® vaccination and HIN1 influenza infection [7–10].

Since the early descriptions, NT1 has been depicted as a distinct neurological disorder characterized by disruption of the normal sleep-wakefulness rhythm [11] and loss of boundaries between sleep and wake, with frequent state transitions and intrusions of REM sleep (or REM sleep elements) into the other ongoing states of being [12–14]. NT1 is a lifelong disorder, mainly arising during childhood [2, 14] and early adulthood [1], with a common diagnostic delay of many years after the onset of symptoms [2, 15, 16].

Among the pentad of NT1 clinical manifestations, cataplexy is considered to be the pathognomonic sign of NT1. Disrupted nocturnal sleep, however, is as much a prominent feature as daytime symptoms. Indeed, since the early 1960s, nocturnal sleep disruption and increased motor activity during sleep have been reported as prominent and even temporally preceding the other symptoms [17, 18]. Pioneering polysomnographic (PSG) studies, performed in the 1960s, pinpointed the peculiar aspect of persistence of wakefulness chin and limb EMG activity into REM sleep of both untreated and medicated narcoleptic patients [19]. This condition was named as intermediate or ambiguous sleep and also labeled as sleep stage VII [19–21]. Accordingly, after the discovery of REM sleep behavior disorder (RBD), narcolepsy was immediately recognized as one of the conditions associated with RBD [22]. Nowadays, RBD is reported to occur in NT1 [6] with a frequency ranging between 7 and 63% in different cohorts [22–25].

Neurophysiological investigation of sleep in NT1 has also grown [7, 26–33], and several studies have now focused on the neurophysiological and on the phenomenological descriptions of pathological movements and behaviors occurring during REM sleep [22, 23, 34–38]. Currently, the ICSD-3 recognizes that RBD in NT1 patients represents “another form of REM sleep motor-behavioral dyscontrol” different from that observed in the RBD type associated with synucleinopathies (namely, Parkinson disease, multiple system atrophy, and Lewy body dementia). “RBD associated with narcolepsy” indeed is “characterized by lack of sex predominance, less complex and more elementary movements in REM sleep, less violent behavior in REM sleep, earlier age of onset, and hypocretin deficiency” [6]. In NT1 “RBD may be precipitated or worsened by the pharmacological treatment of cataplexy” (namely, antidepressants) and “in pediatric patients may be an initial manifestation of NT1” [6]. Data on a possible phenoconversion of NT1 patients with RBD into dementia and/or dysautonomia are lacking, although the cross-sectional studies on NT1 seem to be reassuring, since no increased risk to develop neurodegenerative diseases and dysautonomia has been reported in elderly NT1 patients. One case report describes the appearance of RBD followed by Parkinsonian signs in an adult NT1 patient. RBD was recognized to develop independently from NT1 in the presence of an autoimmune disorder (rheumatoid arthritis) as a possible risk factor for both conditions [39]. The present stage of investigation, indeed, seems to indicate that RBD, as with all the other NT1 symptoms, may accompany NT1 patients for life, with variable penetrance and severity but without a worsening trend.

11.2 REM Sleep Behavior Disorder in Narcolepsy: Definition

RBD is characterized by abnormal behaviors emerging during REM sleep associated with excess of EMG muscle tone and/or phasic twitching during REM sleep [6]. According to the ICSD-3 [6], for the diagnosis of RBD, criteria A to D must be met: (A) repeated episodes of sleep-related vocalization and/or complex motor behaviors; (B) these behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep; (C) polysomnography demonstrates REM sleep without atonia (RWA); and (D) the disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

Although the above criteria mostly refer to the idiopathic form of RBD and forms eventually developing synuclein-associated degenerative disorders (Chaps. 5 and 6), they are also fully applicable for the diagnosis of RBD associated with narcolepsy and mainly NT1.

The association of RBD and narcolepsy has been considered as one of the multifaceted aspects of REM sleep motor dyscontrol of narcolepsy and was reported since the earliest RBD discovery and descriptions [19, 22, 23]. Despite a not negligible rate of discrepancy, several reports are convergent to identify a high frequency of RBD in NT1 adult patients. Overall, narcolepsy seems to be the second most frequent condition associated with RBD, after the neurodegenerative diseases, and approximately accounts for 10–15% of all patients affected by RBD [41].

Studies based on clinical interview and/or questionnaires detected a higher prevalence of suspected RBD (45–61%) when contrasted with the PSG-based reports in narcoleptic patients (36–43%) [22–24, 35, 36, 42, 43]. Discrepancies arise from both selection and recruitment biases, namely, small numbers of patients, lack of controls, inclusion/exclusion of sleep-related injury or parasomnias, inclusion/exclusion of patients without cataplexy, inclusion/exclusion of medicated patients, and on methodological issues. Indeed, many studies are based on questionnaires or semi-structured clinical interviews that are not always coherent with the ICSD-3 criteria. Even when PSG is available, the lack of a specific threshold for a definition of RWA in narcolepsy does not allow a clear interpretation of the results [35, 36, 42, 44, 45].

Indeed, some studies on NT1 cases pinpoint that even in the absence of a clinical complaint of RBD, video-PSG may reveal an excessive increase in chin EMG tone or excessive limb or chin EMG twitching during REM sleep or infrequent, simple motor behaviors without any history of injurious or disruptive sleep behaviors [36, 45]. The latter milder form of RBD may have remained undetected to result in an underestimation of RBD in narcolepsy [36]. This leads to the important and unresolved issue of what are the most minimal RBD diagnostic criteria: at what point does RWA/subclinical RBD end and clinical RBD begin? Future night-to-night variability studies on the atonia index in NT1 patients with and without RBD would contribute to clarify whether RWA fluctuates or is a stable trait in the patient group with RBD, (likewise in idiopathic RBD), permitting RBD episodes to surface. The differences between clinically reported RBD and (video)-PSG-detected episodes of

REM-related acting-out dream motor activity in NT1 indicate on the one hand that RBD is not manifested every night in these patients and on the other hand that a milder form of RBD could often be overlooked by patients and their bed partners in the context of a wider, polymorphic, and dramatic nighttime sleep disruption that affects NT1 patients. In this context, it is important to underline that also NT1 patients without clinical RBD episodes have been reported to present a milder degree of RWA that is mainly represented by phasic, rather than tonic, EMG activations [28].

11.3 REM Sleep Behavior Disorder in Narcolepsy: The Adult Phenotype

Generally, the behaviors during RBD episodes in narcoleptic patients are less violent toward bed partners/themselves than in idiopathic RBD and RBD associated with synucleinopathies [3, 23, 25, 43, 46, 47]. Thus, they rarely cause traumatic or forensic consequences. However, a case of violent sleep-related behavior in a NT1 patient with RBD, causing injuries to his wife and resulting in the charge of assault and contributing to divorce, has been reported [3].

Several clinical aspects may help to differentiate RBD of narcoleptic patients from idiopathic RBD. In NT1 cases, RBD can arise early in the patient's life, without sex preference, and may be modified by narcolepsy treatment. In general, RBD is not a primary complaint in NT1 patients and is often comorbid with a number of sleep disorders that frequently affect patients with narcolepsy. A video-PSG study indicated a high proportion of RBD (namely, 43%), in drug-naïve adult NT1 patients regardless of the frequency of cataplectic attacks and their sex [42]. Some studies also indicate that the phenotypic clinical RBD manifestations in narcolepsy range from increased muscle twitching and jerks to complex, organized, and purposeful motor and verbal activities leading to an enacted dream behavior [25, 36]. Moreover, RBD is not an every-night phenomenon in NT1 patients with clinically relevant RBD, and 24-h video-PSG recordings indicated that RBD episodes tend to occur with comparable frequency in the first part and in the second part of the night [42] and in any REM sleep period, including sleep-onset REM periods in daytime naps (Fig. 11.1) [48], and display less violent/aggressive features when they occur in the first half of the night [35]. Interestingly, in NT1 subjects, during RBD episodes there can also be observed cataplexy [49] and other dissociated REM-dreaming phenomena such as volitional control and awareness of dreaming, flying experiences, and out-of-body experiences [48], indicating the co-occurrence of several dissociated mental and motor features of REM sleep during the same RBD episode [37].

A significantly increased amount of REM sleep-related simple movements at video-PSG analysis has been pinpointed also in drug-naïve NT1 patients without clinical RBD, when compared with those with clinical RBD [35]. This finding expands the role of video-PSG for the diagnosis of RBD in narcoleptic patients and indicates the need of more detailed video-PSG diagnostic criteria [50]. (This important topic is discussed in Chap. 45.) The greater amount of the above-described simple movements during REM sleep in NT1 cases with RBD, indeed, may be

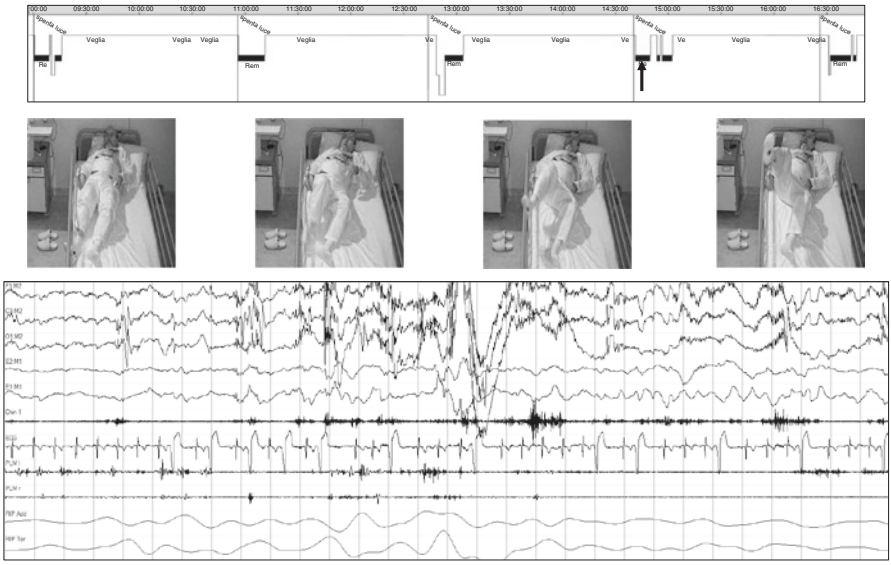

Fig. 11.1 *First line (from the bottom)*: Hypnogram of the multiple sleep latency test in a 64-year-old NT1 male patient presenting an episode of RBD during a sleep onset in REM sleep. *Second line*: Photograms indicate the energetic behavior performed while in REM sleep: the patient was trying to kick somebody with his right foot in his dream. *Third line*: (PSG findings) two 30-s REM epochs while the patient was performing the complex episode, showing increased phasic activity over the mylohyoideus muscle and over the left and right tibialis anterior EMG channels

considered for future diagnostic criteria, in addition to quantitative EMG analysis [28], as a candidate hallmark for the confirmation of the clinical diagnosis of RBD in narcoleptic patients, in whom it is difficult to capture a full-blown/clear-cut RBD episode with a single night of video-PSG, and it is also problematic to rely on the subjective reports of RBD episodes collected by the patients or on the questionnaires compiled by bed partners.

11.4 REM Sleep Behavior Disorder in Narcolepsy: The Childhood Phenotype

Despite NT1 being a lifelong disorder arising mainly in children and adolescents [1], with around 5% of cases occurring in prepuberty [51], the phenomenology of abnormal movements and behaviors occurring during sleep in children with NT1 has been scarcely investigated. Anamnestic recall coming from the parents and from the young patients themselves usually highlights that children, close to the disease onset, have a markedly disturbed nocturnal sleep with continuous movements and nightmares that could be reminiscent of RBD. Despite this clinical evidence, only recently RBD has been systematically assessed in children with NT1 [38]. Indeed, there are only a few earlier papers reporting RBD in NT1 children, which might

have been erroneously interpreted as if RBD was a rare phenomenon in NT1 children [52–56].

Antelmi and coworkers, by analyzing video-PSG and video-multiple sleep latency test (MSLT) recordings in a controlled cohort of children affected by NT1 and matched healthy controls, characterized in detail their motor behaviors during sleep and highlighted the striking presence of motor dyscontrol affecting sleep [38]. The study pinpointed that the number and index per hour of elementary movements occurring during REM sleep are greater in the young NT1 patients when compared to controls and that complex behaviors in REM sleep (full-blown RBD episodes) are detectable only in NT1 patients (32.5% of the patients). Despite being so frequent, only one patient had a violent and energetic behavior, raising up the head and the trunk and shaking the arms, in a fashion similar to the episodes observed in adult NT1 patients [35, 36]. In many NT1 children, the RBD-related behaviors ranged from the "acting out" of a dream to almost continuous/subcontinuous "pantomime-like" activities. These latter episodes usually consisted in calm, repetitive, and slow gesturing, resembling purposeful behaviors or reminiscent of lively interactions with the environment and/or with persons. Also in children with NT1, as already reported in adults [35, 36], RBD episodes are not restricted to REM sleep of the latter part of the night but occur during every REM sleep period throughout the night (more than once per night) and even during sleep-onset REM sleep periods during nocturnal PSG and during the MSLT procedure [38] (Figs. 11.2 and 11.3).

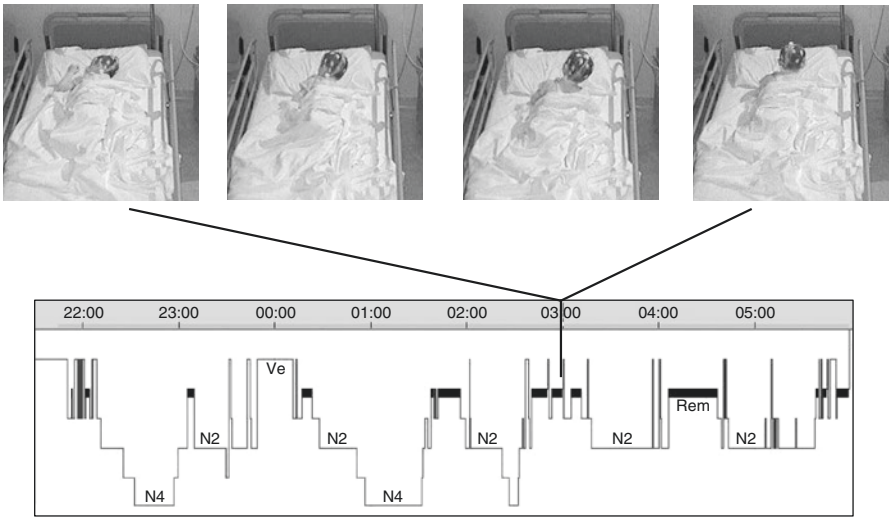

Fig. 11.2 Hypnogram of the nocturnal polysomnography in a 5-year-old NT1 male patient who presented an episode of RBD, occurring in the second half of the night. Legend: *Ve* wakefulness, *Rem* REM stage, *N1* stage 1 of NREM sleep, *N2* stage 2 of NREM sleep, *N3* stage 3 of NREM sleep, *N4* stage 4 of NREM sleep. Photograms above the hypnogram show the video capture of the episode. The child raised up his head and trunk and screamed out, calling his mother

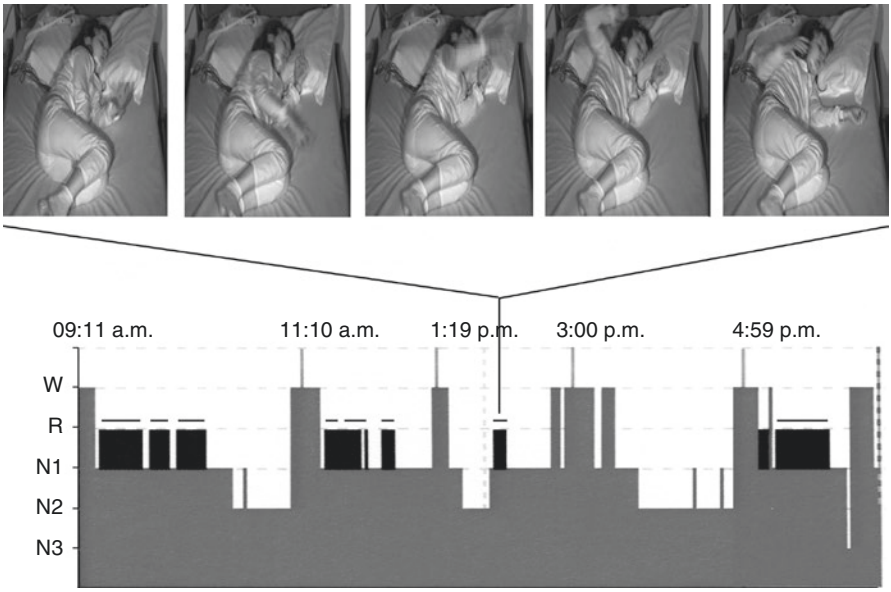

Fig. 11.3 Hypnogram of the multiple sleep latency test in an 8-year-old NT1 female patient with subcontinuous complex episodes ("pantomime-like") during REM sleep. Legend: *W* wakefulness, *R* REM stage, *N1* stage 1 of NREM sleep, *N2* stage 2 of NREM sleep, *N3* stage 3 of NREM sleep; bars above the hypnogram indicate the occurrence of the complex behaviors. Photograms above the hypnogram show an example of the calm subcontinuous movements

Overall, in NT1 children, RBD seems to be a very common pattern if compared with the available adult studies (note that a controlled study in adults is still lacking). Noteworthy, NT1 children with RBD, despite a comparable sleep structure to those NT1 patients without RBD, complain of a greater amount of excessive daytime sleepiness and impaired nocturnal sleep, indicating that RBD in childhood NT1 is associated with greater narcolepsy disease burden. NT1 children with RBD also had significantly higher rates of cataplexy during the daytime, underlining the importance of routine objective assessment of RBD in these cases as a disease severity index. Finally, RBD can also be a symptom forerunning the development of full-blown NT1 in children [54].

11.5 REM Sleep Behavior Disorder in Narcolepsy: Neurophysiological Findings

A global impairment of motor control in REM sleep appears to be an intrinsic finding of narcolepsy, in particular in the context of NT1 [28, 45]. We may hypothesize that inhibitory systems of motor regulation are globally damaged in narcolepsy and that this may be related to hypocretin (orexin) deficiency. The motor dysregulation of NT1, although probably not exclusively, is predominant in REM sleep and leads

to a constellation of different dissociated REM-wakefulness states, namely, cataplexy, sleep paralysis, RWA, and RBD.

RWA and RBD are often accompanied by an elevated periodic limb movement index, in NREM sleep as well as in REM sleep in NT1 cases [37, 38]. This excessive motor activity during REM sleep observed in NT1 may reflect an instability of REM sleep motor regulation. Besides RWA, PSG studies from patients with NT1 reported frequent shifts from REM to NREM sleep and mixed features of REM and NREM sleep stages simultaneously, such as the presence of atonia in N2 sleep and/or the presence of sleep spindles in REM sleep leading to ambiguous sleep [28, 36, 40, 42, 45].

RWA is the neurophysiological hallmark of RBD and is polygraphically defined by an excessive amount of sustained or intermittent elevation of tonic chin EMG activity and/or excessive phasic submental or limb EMG twitching during REM sleep. The severity of RWA in patients is quantified with visual [58–60] or automated [43, 61–63] analysis of chin and limb EMG tracings. (This topic is covered comprehensively in Chaps. 18 and 31 and in Chap. 46 as a future clinical and research perspective.)

Only few studies have applied the visual quantitative approaches developed for the scoring of RWA to the study of narcolepsy. The quantitative approach formerly proposed by Lapierre and Montplaisir in 1992 [58] was then revised in 2010 [64]. This method scores each REM sleep epoch as tonic or atonic depending on whether tonic chin EMG activity is present for more or less than 50% of the epoch. Another approach proposed by the SINBAR group recommends the use of quantification of any type of EMG activity, irrespective of whether it consisted of tonic, phasic, or a combination of both EMG activity from the chin EMG tracing and phasic EMG activity from the right and left flexor digitorum superficialis muscles [59]. According with the method of Lapierre and Montplaisir [58], patients with narcolepsy may differ from patients with idiopathic RBD [44]. In particular, patients with narcolepsy present a higher percentage of REM sleep without atonia and an increased density of phasic chin EMG activity during REM sleep, when compared to normal controls. This picture could distinguish narcoleptic patients from patients with idiopathic RBD. The latter, indeed, have a higher prevalence of RWA than narcoleptic patients and controls [45]. According to the above studies, 50% of patients with narcolepsy and 87.5% of patients with idiopathic RBD, respectively, exceeded the 20% threshold of RWA, displaying an abnormal REM sleep muscle activity [45].

A computer quantitative analysis-based method, describing both persistent and transient modifications in chin EMG amplitude during sleep, has been validated in normal controls, across their life span, in idiopathic and symptomatic RBD [43, 62, 65, 66] and NT1 patients [28]. Thresholds of the REM sleep atonia index [28] have been validated for all the above groups and also for patients with NT1 with and without clinical and video-PSG diagnosis of RBD, compared to age-matched normal controls, showing that this computerized automatic analysis may detect subclinical signs of RBD on PSG recordings (Fig. 11.4). Another study suggested that the increased REM sleep muscle twitching could be a differential feature of NT1 cases with RBD, showing that an altered REM sleep atonia index in patients with NT1 is mostly due to an increase in short-lasting EMG activity, and this finding may differentiate NT1 patients with RBD from other forms of RBD [25].

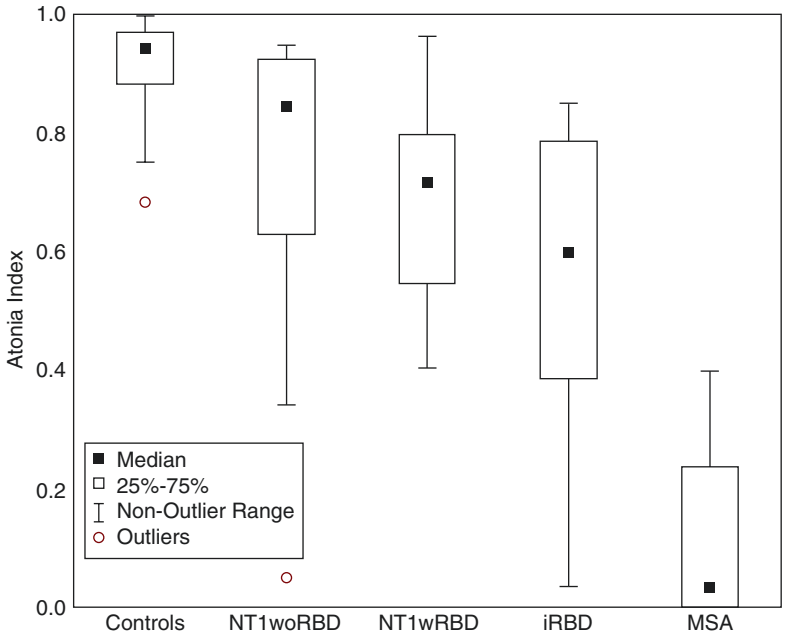

Fig. 11.4 Atonia index. REM sleep atonia index in normal controls, patients with NT1 without RBD (NT1woRBD), patients with NT1 and RBD (NT1wRBD), patients with idiopathic RBD (iRBD), and patients with multiple system atrophy (MSA) (data from Ferri et al. [28, 62]). Values are shown as median (black-filled squares), 25–75% quartiles (boxes), non-outlier range (whiskers), and individual outlier values (circles)

Overall, NT1 patients with and without a clinical complaint of RBD disclose an elevated chin EMG activity irrespective from the visual quantitative or computerized methods of analysis used, but not all the studies based on the visual quantitative analysis detected a signal of a more elevated chin EMG activity in NT1 patients with RBD when compared with those without. This indicates that the occurrence of RBD episodes appears less predictable in NT1 patients than in other RBD patients, although a higher prevalence of REM sleep-related EMG activation has been found in patients with documented RBD compared to patients without RBD. Overall, in the absence of clinical RBD symptoms, RWA scores are still debated tools for a reliable prediction of RBD episodes in NT1 [22]. Data on a large population of NT1 patients, however, indicate that RWA correlates not only with abnormal motor activity during REM sleep but also with lower hypocretin levels [25].

Also in NT1 children, it has recently been reported that the REM sleep atonia index [28] was significantly decreased in NT1 children with RBD versus those without RBD, thus being the strongest neurophysiological marker of this often overlooked associated disorder [38]. In children with NT1, RWA index has been proposed as a diagnostic biomarker, since it displays high sensitivity and specificity when contrasting NT1 with other central disorders of hypersomnolence [67].

As mentioned above, altered motor control of NT1 sleep is not restricted to REM sleep. First of all, an atonia index lower than that of controls was reported in NT1

patients not only during REM sleep but also during NREM sleep, as opposed to idiopathic RBD patients who showed lower atonia index during REM sleep but higher atonia index during NREM sleep (especially slow-wave sleep) than normal controls. This further expands the neurophysiological difference between RBD in NT1 and in idiopathic RBD [68].

Moreover, NREM parasomnias are reported to be frequent in narcoleptic children [23, 34]. Noteworthy, both adult NT1 patients [27, 35, 41, 68] and NT1 children display an elevated PLMS index [38, 69–71]. In NT1 patients, PLMS indices are higher both in NREM and REM sleep, and the difference is greater for REM sleep when compared to healthy matched controls [27]. The PLMS index increases with age in both narcoleptic patients and controls and may have an impact on sleepiness [27, 68]. However, when patients with concomitant restless leg syndrome (a condition that may affect approximately 15% of narcoleptic patients [72]) are not included, the PLMS index drops significantly in patients with NT1 alone [73].

11.6 REM Sleep Behavior Disorder in Narcolepsy: Pathophysiology

Circumscribed electrolytic lesions of tegmental pontine structures in cats made by Jouvet and coworkers in the1960s eliminated the electromyographic atonia during paradoxical sleep, generating abnormal REM sleep without atonia, with dramatic behavioral consequences during REM sleep in the animal [74]. These finding was further replicated by lesional studies in rats [75]. Thanks to these observations, Schenck, Mahowald, and colleagues recognized the human equivalent of the animal model in their discovery of RBD [76], a disorder characterized by pathological release of muscle tone and behavior during REM sleep, leading to dream-enacting motor behavior.

In cat studies, depending upon the area damaged, progressively extending from the dorsal pontine tegmentum to the midbrain and to the central nucleus of the amygdala [77–79], when entering into REM sleep, the animals exhibit different behaviors, from head lifting to predatory attacks. In contrast, bilateral pontine tegmental lesions release a state of REM sleep without atonia with a minimal increase of motor manifestations. The detailed anatomical study of lesional experiments in animals has identified independent pathways in brain stem that mediates the atonia and EEG phenomena of REM sleep [80]. Accordingly, selective brain stem damage may lead to particular dysfunction with occurrence of independent/dissociated REM sleep features, with loss of REM sleep atonia and with persistence of REM sleep EEG phenomena [80]. NT1, in humans, is caused by the loss of hypocretin (orexin) neurons within the lateral hypothalamus [81, 82].

Hypocretin neurons are excitatory and active during wakefulness with strong projections to the brain stem structures implicated in REM sleep motor modulation. A decreased hypocretinergic tone due to the loss of hypocretin producing neurons in NT1 may cause atonia during wakefulness, leading to cataplexy, and to the loss of muscle atonia and RBD in REM sleep. Moreover, a dysfunction of the amygdala has also been

suggested in NT1. Several functional studies, indeed, are convergent in identifying an amygdala-hypothalamic dysfunction during wakefulness and during cataplexy in NT1 patients [83], which could help explain the mechanisms of emotional triggers of cataplexy. Hence, we may suppose a wide and complex network dysfunction responsible for RBD and cataplexy, unique to narcolepsy. In secondary and idiopathic RBD, the persistence of REM sleep with muscle tone and/or RBD may be the consequence of direct lesions in the subcoeruleus region, which has not been reported in NT1. Although hypocretin network dysfunction is crucial for NT1, it remains unclear how in these patients hypocretin deficiency might cause RWA, cataplexy, and RBD.

Although RWA is among the diagnostic criteria for RBD [6], and it is a clear-cut marker for idiopathic RBD [84], much less is known about RWA in NT1 patients [22]. Moreover, there is still uncertainty as to whether in these patients the extent of RWA depends on the concomitant occurrence of RBD [28]. However, even if differences exist between RBD in narcolepsy and in neurodegenerative conditions, and in the RBD idiopathic form, its presence could also suggest the involvement of common neurochemical and neurophysiological mechanisms. Pharmacological, brain imaging and neuroendocrine findings suggest that RBD and PLMS are related to impaired brain dopaminergic transmission [44, 45, 85–87]. Dopaminergic abnormalities are critical downstream mediators of hypocretin deficiency, and dysfunctions in the hypocretin/dopaminergic system are likely to be important mechanisms involved in the pathophysiology of NT1. Hypocretin deficiency predicts the association between PLMS in REM sleep and RBD [45], suggesting that PLMS and RBD are pathophysiologically intrinsic to NT1 and possibly linked to the hypocretin system dysfunction.

11.7 Management of REM Sleep Behavior Disorder in Narcolepsy

Since the early reports on PSG studies of narcoleptic patients, various authors [19–21] have pinpointed the need for a careful evaluation of the current treatment of cataplexy. Tricyclic antidepressants (e.g., clomipramine) indeed may induce RWA, but also serotonergic, noradrenergic/serotonergic drugs may induce RBD [40, 85, 88, 89]. Since RBD is not listed among the narcolepsy symptoms, there are no available reports of prospective, double-blind, placebo-controlled trials of any specific drug to treat RBD in narcolepsy.

Idiopathic RBD patients often require pharmacological treatment. Clonazepam is widely considered to be the most effective drug for idiopathic and secondary RBD [90–92]. However, only a few case reports of narcoleptic patients with RBD treated with clonazepam have been published [88, 91]. Since RBD is rarely a primary complaint in NT1, a medication to treat RBD is not often required in these patients; other limitations to the use of clonazepam are represented by the relative contraindications to the use of a sedative benzodiazepine in conditions that are often comorbid in NT1 patients, namely, obstructive sleep apnea syndrome, increased daytime sleepiness, and depression. Also melatonin has been proposed in patients affected with RBD, with some benefits [93–96], as discussed in Chap. 24.

Given the beneficial effects of sodium oxybate on disturbed nocturnal sleep in patients with NT1 [97], isolated reports indicate a remarkable improvement also of RBD episodes in patients with NT1 [98]. Although clinical experience by others and a reanalysis of the results of a multicenter study on sodium oxybate by a semi-automatic analysis of chin EMG suggested that sodium oxybate could be effective to treat clinical RBD in NT1 [99], no systematic study has ever been conducted on the treatment of RBD in NT1 [100]. Therefore, controlled trials using clonazepam, melatonin, or sodium oxybate are warranted to arrange guidelines for the treatment of RBD in the context of NT1 [85, 98, 99, 101–104]. (Chapter 25 reviews the literature on sodium oxybate therapy of RBD.)

Conclusions

Nighttime and daytime sleep of patients with narcolepsy is often severely disrupted by alterations in the NREM/REM cycles, awakenings, and sleep/wake motor dysregulation, resulting in PLMS, RWA, and RBD [105], with the latter two conditions being most pronounced in patients with NT1. RBD, indeed, is a frequent symptom in NT1: motor behavioral phenomena are usually milder when compared to that of idiopathic RBD; they may appear during every REM sleep periods and also during sleep-onset REM periods in daytime naps. RBD may be observed at any age in NT1 patients, but it is rarely a primary complaint for patients, although the REM sleep motor manifestations are often an impressive video-PSG finding, especially in NT1 children. RBD in NT1 seems to have a different pathophysiology from that of idiopathic RBD, and it does not seem to represent a marker of impending synucleinopathies. The high frequency of RBD in NT1, indeed, is a plausible result of the decreased hypocretinergic activity input to brain stem structures that may contribute to dissociated sleep/wake states and motor disinhibition during REM sleep.

RBD in NT1 therefore, along with the cardinal symptoms of NT1, can be defined as one of the manifestations of state dissociations [37]. Since the RBD episodes are not every-night phenomena in NT1, diagnosis should rely on the clinical history, on the careful analysis of RWA, and on video-PSG that often display an increase of elementary movements during REM sleep in NT1 patients with RBD, mainly in children. In children with NT1, indeed, RBD is probably more severe than that reported so far in NT1 adults. Noteworthy, in these children, RBD seems to be part of a complex motor instability resulting in cataplexy when emerging from wakefulness, up to a focal subcontinuous cataplectic condition, namely, "cataplectic facies" [106], and from sleep, with complex motor behaviors occurring in REM sleep [36, 38]. Nevertheless, since RBD in NT1 appears to be a dissociated wake-REM sleep manifestation, like cataplexy, sleep paralysis, and hallucinations, further research on the clinical significance and on the prognostic value of RBD and RWA is needed, in particular, focusing on the relationship of RBD and dysautonomic signs, namely, the arterial blood pressure nocturnal non-dipping profile described in narcolepsy [107], on the impact of RBD on narcoleptic daytime symptoms and on its treatment.

Note Added in Proof: The following is a recent pertinent publication: Bin-Hasan S, Videnovic A, Maski K. Nocturnal REM sleep without atonia is a diagnostic biomarker of pediatric narcolepsy. J Clin Sleep Med. 2018;14:245–52.

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Acute REM Sleep Behavior Disorder

12

Federica Provini and Naoko Tachibana

12.1 Introduction

The concept of RBD has changed since its first description in 1986 [1]. Although RBD is usually considered to be a chronic parasomnia affecting primarily older men and with a close relationship with degenerative neurological conditions, there is an increasing body of literature reporting cases of acute or subacute RBD, occurring irrespective of age and sex. RBD, or isolated REM sleep without atonia (RSWA), has been associated with various medications or substances, in particular antidepressants, and with the abrupt withdrawal from barbiturates, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and alcohol. Less frequently, structural brain lesions (vascular, demyelinating disease, tumors), especially in the pontine region, may cause RBD. RBD can appear acutely after a stressful life event and in post-traumatic stress disorder (PTSD). This chapter focuses on these incidental forms of secondary RBD, in which RBD does not appear as a classic clinical feature of the underlying conditions, but rather as an unexpected epiphenomenon. Apart from the importance of RBD recognition and management in these clinical conditions, acute RBD manifestations could also have crucial importance in understanding the full spectrum of the pathophysiology of RBD [2].

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12.2 RBD and Drugs

12.2.1 Antidepressants

An association with most classes of antidepressants has been implicated in RBD and RSWA, but never bupropion, a dopaminergic-noradrenergic agent [3–7].

Tricyclic antidepressants and fluoxetine cause changes in sleep architecture and polysomnographic (PSG) findings, causing abnormal, prominent eye movements during non-REM sleep and suppressing REM sleep [8, 9]. In 11 young adult subjects who underwent 3 nights of PSG recordings after administration of 25 or 50 mg of clomipramine, or non-active placebo, clomipramine induced tonic mentalis EMG activity during REM sleep [10]. Winkelman and James [3] demonstrated that tonic, but not phasic, submental EMG activity during REM sleep was significantly more common in the 15 subjects taking serotonergic antidepressants than in the 15 age-matched individuals not on such medication. Sertraline (50–200 mg/day) may induce or exacerbate tonic and phasic RSWA as shown in an 8-week open-label trial in 31 depressed patients. In contrast to idiopathic RBD, sertraline-related RSWA had the specific characteristics of being correlated with the degree of the prolonging of REM latency without any predominance of male sex and elder age, suggesting possible different pathophysiological mechanisms [11]. Sertraline-induced RBD was reported in an 87-year-old male veteran treated for PTSD, who was also taking bupropion and lorazepam. RBD completely disappeared upon sertraline discontinuation and returned within 1 month of restarting sertraline [12].

Although most reported data are case reports or case series, there are no controlled studies showing that antidepressants cause frank RBD, nor are there studies comparing PSG findings before and after the initiation of antidepressants in the same subjects. In contrast, multiple groups have reported individual patients who developed RBD after initiating treatment with antidepressants [13–16].

In some cases of narcolepsy, clomipramine hydrochloride improved the cataplexy and partially alleviated the daytime sleep attacks, but resulted in episodes of severe motor hyperactivity during sleep, which were most intense during REM sleep [13, 17]. Olson et al. in reviewing 93 cases of RBD found that in only one patient (who also had Parkinson's disease) RBD developed at about the same time when medication (amitriptyline) was commenced [18].

Fluoxetine has been found to be similar to the tricyclic antidepressants in its capacity to induce clinical or subclinical RBD, as first reported in 1992 by Schenck et al. [9]. In a retrospective review of adults undergoing PSG while taking antidepressants, 93 consecutive adults were treated with fluoxetine or tricyclic antidepressants. Among them the authors reported the case of a 31-year-old man with obsessive-compulsive disorder (OCD) who developed RBD shortly after starting fluoxetine therapy, which persisted at PSG study 19 months after fluoxetine discontinuation. In this fluoxetine-induced RBD, the history provided by the patient's wife virtually excluded any preexisting parasomnia, and the dream disturbance was very typical for RBD and did not incorporate any of the patient's OCD activity. After that initial case, some other case reports documented RBD that was clearly associated

with the use of fluoxetine and then paroxetine [16] and venlafaxine [19]. Fluoxetine also probably aggravated a mild form of RBD in a case of voltage-gated potassium channel antibody-associated limbic encephalitis (VGKC-LE) [20].

Mirtazapine was associated with RBD in four patients with parkinsonism, which was then resolved after the drug was discontinued [21]. Two large retrospective studies seem to suggest that a unique clinical profile exists with a strong association among antidepressant use, early-onset RBD, female sex, and younger age, while usually RBD is typically seen in older men [22, 23]. Although there are associations between antidepressants and RBD, and also between psychiatric disease and RBD, the interrelationships and causalities remain to be more fully elucidated, as discussed in Chap. 10. The current literature suggests that antidepressants are not likely to be the sole causative agent, both for older adult and especially for younger adult onset RBD. Probably a complex mechanism with both predisposing individual vulnerabilities and precipitating effects from the use of antidepressants is involved.

Most patients prescribed with an SSRI, SNRI, TCA, or MAOI antidepressant do not develop RBD. Literature data in psychiatric patients (pRBD) seem to document that RBD may be related to a constellation of factors, including individual predisposition, and the presence of a depressive illness, instead of RBD being merely secondary to antidepressants [24–27]. A clinical epidemiological study conducted in a psychiatric outpatient setting found that the risk of developing RBD among those taking SSRI antidepressants was only about 1 out of 20 [24]. A follow-up study of the psychiatric patients with RBD features was subsequently conducted by ceasing or switching SSRI to other classes of antidepressant [25]. Clinical and PSG reassessment after 6 months of intervention reported a partial improvement of the RBD symptoms, but the PSG feature of REM atonia was not fully restored [25]. It is also possible that antidepressants unmask latent RBD rather than cause it. On the other hand, in some cases RBD dramatically improved with SSRIs and deteriorated with a 5-HT_{1A} partial agonist, tandospirone, and acute RBD appeared during withdrawal from imipramine [28, 29].

The intriguing relationship between depression and RBD was further investigated by evaluating if RBD with antidepressant use can be an early signal of an underlying neurodegenerative disease. To address this possibility, Postuma et al. [6] analyzed a cohort of 100 idiopathic RBD (iRBD) patients in order to understand whether RBD occurring with prescription of antidepressants is a relatively benign side effect or is a marker of prodromal neurodegenerative disease that requires further evaluation and follow-up. In their interesting prospective cohort, 27 patients were taking antidepressants. Compared to matched controls, RBD patients taking antidepressants demonstrated abnormalities indistinguishable in severity from RBD patients not taking antidepressants, and, in a prospective follow-up, RBD patients taking antidepressants had a lower risk of developing neurodegenerative disease during the follow-up period than those without antidepressant use. However, although patients with antidepressant-associated RBD had a lower risk of conversion to neurodegeneration during the follow-up period than patients with "purely idiopathic" RBD, markers of prodromal neurodegeneration (such as olfaction impairment, systolic blood pressure drop, constipation, depression, etc.) were

clearly present. The conclusion from this study was that the antidepressants accelerated the emergence of RBD in patients already in the early stages of alpha-synucleinopathy neurodegeneration, without accelerating the emergence of the neurodegeneration.

12.2.2 Other Drugs and Substances

Some reports suggested that other agents may play a role in inducing acute RBD. In 1995 Louden et al. reported three non-demented PD patients who manifested RBD while on recommended doses of selegiline. None of them had problems severe enough to suggest RBD while they were being treated with varying doses of other dopaminergic agents (carbidopa/L-dopa, pergolide) unaccompanied by selegiline [30]. Phenelzine, another MAOI, can induce RBD in healthy young subjects [31], but at the same time parnate, another MAOI, suppressed behavioral manifestations in a patient with iRBD [32]. Carlander et al. documented RBD in a 62-year-old man with Alzheimer's disease (AD) induced by the acetylcholinesterase inhibitor rivastigmine (SDZ-ENA 713) during a phase III clinical trial, at a dose of 8 mg daily. RBD subsided on discontinuation of the treatment [33]. Another 88-year-old man with probable AD (without pathological confirmation) developed RBD after increasing the nightly dose of rivastigmine, from 1.5 to 3 mg (total daily dose, 4.5 mg), as therapy for his dementia [34]. The underlying brain substrate appears to play a crucial role in whether cholinergic therapy will induce RBD, although the mechanism of action remains unclear. On the other hand, in a few cases, cholinergic therapy of iRBD with the acetylcholinesterase inhibitors (AIs) donepezil or rivastigmine was reported to be effective [35]. Twenty-five milligrams of quetiapine (an atypical antipsychotic drug) per night added to chronic fluoxetine therapy (40 mg per day) was reported to cause RBD in a 55-year-old woman [36].

Finally, beta-adrenergic blockers such as bisoprolol [37] and propranolol [38] and heavy caffeine abuse may possibly induce RBD [39]. Another report linked heavy caffeine use and RBD in a patient with prolific coffee intake [40]. Chocolate ingestion even of modest amounts seemed to exacerbate RBD in a single patient [41].

12.2.3 Drug or Substance Withdrawal: PSG Studies in Pre-RBD Days

RSWA and an acute, transient, form of RBD induced by abrupt withdrawal from barbiturates [42], meprobamate [43], pentazocine [44], nitrazepam [45], MAOI (phenelzine) [46], and ethanol have been well documented [47–49].

Barbiturates, phenelzine, and ethanol rapid withdrawal can induce a rebound of REM sleep during which motor paralysis is breached, muscle tone is regained, and dreams are acted out. Hence, this is the so-called REM intrusion or "spillover" theory of drug withdrawal psychosis or acute delirium first proposed and elaborated by Dement and Fisher [46] and Gross [47].

Delirium tremens (DTs) represent the most severe complication of alcohol withdrawal syndrome, appearing after a significant reduction or complete discontinuation of alcohol consumption in patients suffering from chronic alcohol dependence. DTs are characterized by features of alcohol withdrawal itself (tremor, motor violent agitation, diaphoresis, hypertension, tachycardia, etc.) together with acute-onset severe insomnia, visual hallucinations, and dream enactment. Even though the pathogenetic mechanism of DTs is not fully understood, we can assume that sudden alcohol withdrawal results in a transient homeostatic imbalance within the limbic system, due to the sudden dramatic changes in GABAergic synapses, downregulated by chronic alcohol abuse.

In 1980 Kotorii and colleagues described the sleep pattern of 13 alcoholics who were recorded for 5 consecutive nights after the cessation of alcohol intake. In six of them, DTs occurred. PSG recordings showed a dramatic reduction or absence of synchronized sleep (spindle or delta sleep) even when the disorder did not evolve into DTs. The predominant EEG pattern of alcohol withdrawal consisted in a mixture of stage 1 and REM sleep associated with tonic EMG [48]. This is the same polygraphic pattern described in 1975 by Tachibana et al. who reported that the peculiar sleep pattern of alcoholics who developed DTs was characterized by a concomitant appearance of low-voltage EEG activity, REM burst, and tonic mental EMG. Tachibana et al. called it "stage 1-REM with tonic EMG" reporting that this sleep stage was found also in a meprobamate addict with delirium [43].

12.2.4 Drug or Substance Withdrawal: RBD-Like Phenotype with Different Pathophysiology

Later we observed similar findings in a case of DTs who we followed up for 7 months with serial PSG registrations [50]. During the acute phase of the disease, PSG recordings disclosed a complete sleep-wake disruption with a drastic reduction of spindle and delta sleep and with the presence of an atypical transitional state between REM sleep without atonia and wake, associated with hallucinations and enactment of dream behaviors. We named this condition "oneiric stupor" (OS), with peculiar motor behaviors shown by the patient and characterized by simple stereotyped and repetitive gestures which, on some occasions, could be organized in more complex and quasi-purposeful behaviors mimicking daily-life activities such as dressing, combing the hair, washing, eating, and drinking. Movements performed by the patient during OS mimic the contents conveyed by his dreams, which he was able to recall upon awakening. OS appears not only in DTs but also in fatal familial insomnia (FFI), an autosomal dominant disease caused by a point mutation at codon 178 of the prion protein gene (PRPN), and in Morvan's syndrome, an autoimmune limbic encephalopathy [51, 52]. OS bears some resemblance to RBD, but the two entities are clearly different, as shown in Table 12.1. RBD arises from a normal sleep-wake cycle in which the only abnormality is the lack of muscular atonia during REM sleep. OS, in contrast, arises in a context of severe alteration of the sleep structure with a profound loss of slow-wave sleep and a predominance of a mixed

Table 12.1 Differences between oneiric stupor episodes (OS) and REM sleep behavior disorder (RBD)

Feature	RBD	OS
Timing	At least 60–90′ after sleep onset; usually in the latter part of the night	Throughout the 24 h
Stage	From REM sleep only	Generally from a mixed EEG state with features of both N1and REM sleep
Sleep structure	Normal; REM without atonia	Completely disorganized
Duration	Short	Long
Episode frequency	Usually once per night	Continuous or subcontinuous state
Episode motor pattern	Violent behaviors mimicking the content of a dream	Quiet, stereotyped, and repetitive gestures usually mimicking daily-life activities
Episode dream content	Patients usually report a complex "dream tale" including defense against attack by unfamiliar people or animals	Patients tend to describe a single "oneiric scene," generally neutral

Modified from Guaraldi et al. 2011 [53]

state with features of both stage 1 NREM and REM sleep, as depicted in Fig. 12.1. OS is not restricted to the last part of the night, as with RBD, but occurs throughout the night due to the loss of a physiological sleep structure. OS tends to present in clusters or subcontinuously if the patient is left alone and not stimulated, whereas a complex RBD episode usually occurs once a night [53].

Montagna and Lugaresi of the Bologna group focused on the striking clinical and polygraphic similarities of DT, FFI, and Morvan's syndrome and put forward the concept of Agrypnia excitata (AE) [54]. The prime clinical features of AE are composed of severe insomnia (Agrypnia) coupled with excessive motor and autonomic hyperactivity (excitata). Polygraphically, AE is characterized by the inability to generate the EEG activity typical of deep sleep, viz., delta activity. Remarkably, however, in AE stage 1 NREM sleep is still present, and there is a pathologically increased REM sleep, often with a lack of muscle atonia. The concept of AE thus implies that divergent and actually opposite outcomes pertain to the SWS stages (which disappear) and to light sleep stage 1 (which is conserved and actually augmented). Neuropathologically, the thalamo-limbic circuitry is involved in all of the clinical conditions that exemplify AE [54], and this intralimbic disconnection triggers the generalized activation associated with the inability to sleep [55].

12.3 Acute Lesions

Acute RBD has been observed in humans in association with focal brain lesions damaging the key structures that modulate REM sleep, especially the pontine tegmentum and medial medulla, as shown in Table 12.2. These reports have important

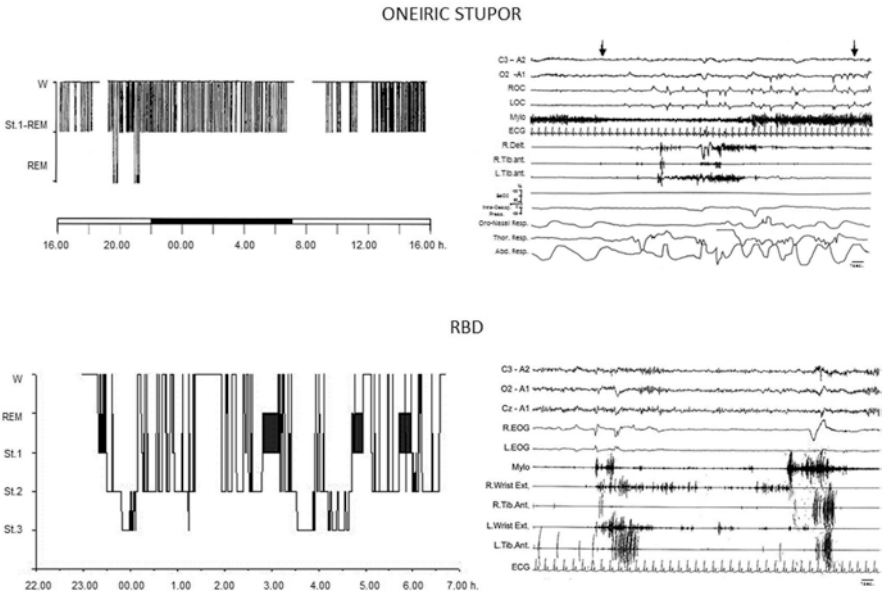

Fig. 12.1 Wake-sleep histograms in an FFI patient with oneiric stupor (top) and in a RBD patient (bottom). Whereas RBD emerges from a normal sleep structure, oneiric stupor arises in the context of a completely disorganized sleep structure with a predominance of a mixed state with features of both stage 1 NREM and REM sleep (N1-REM)

implications for more fully understanding the underlying mechanisms of RBD. Although the preexistence of subclinical RBD cannot be ruled out with full-blown RBD occurring within the context of subacute or acute cerebral dysfunction, in most of the cases, incidental RBD seems to be a de novo event and not an exacerbation of a previously unrecognized RBD. In some cases, it is crucial to establish whether a lesion found in a neuroimaging study is the direct cause of RBD or if it is simply an incidental finding when the imaging was obtained years after the onset of RBD [2]. Iranzo et al. propose five criteria to determine whether a focal structural brain lesion is the direct cause of RBD: (1) RBD onset should be temporally associated with the appearance of the brain lesion; (2) RBD onset should be coincident with the onset of other symptoms caused by the lesion if they do appear (e.g., oculomotor abnormalities, hypersomnia, limbic syndrome, etc.); (3) the lesion should be located in a brain area known to regulate REM sleep (e.g., mesopontine tegmentum, ventromedial medulla, amygdala, hypothalamus, etc.); (4) disappearance of the lesion whenever possible (e.g., by surgery in tumors or by immunotherapy in multiple sclerosis and autoimmune mediated limbic encephalitis) is associated with remission or improvement of the RBD-related nocturnal symptoms and PSG abnormalities; and (5) RBD is not better explained by another current disorder (e.g., Parkinson's disease), medication use, or withdrawal [2].

Small ischemic lesions [18, 56–61], hemorrhages from vascular malformations [2, 62], tumors [63–65], demyelinating plaques [66–68], and inflammatory diseases

Table 12.2 Reported cases of acute RBD: etiological origins

Etiology	Authors (year)	Age (sex)	Lesion type/diagnosis	Lesion location	RBD disappearance/ improvement after etiological therapy (if possible)
Vascular—ischemic	Kimura et al. (2000) [58]	75 (F)	Ischemic infarct	Left paramedian upper pons	
	Peter et al. (2008) [59]	79 (M)	Ischemic infarcts	Bilateral cerebellar and pontine white matter	
	Xi and Luning (2009) [60]	68 (M)	Lacunar ischemic infarct	Right paramedian pons	
	Reynolds and Roy (2011) [61]	67 (M)	Ischemic infarct	Rostral medial pons left of midline	
Vascular—malformation	Iranzo and Aparicio (2009) [2]	81 (M)	Acute hemorrhage from a cavernous hemangioma	Left medulla	
	Felix et al. (2016) [62]	75 (M)	Repeated microbleeds from pontine cavernoma	Midline lower pons	
Tumoral—lesional	Zambelis et al. (2002) [63]	59 (M)	Neurinoma	Left pontocerebellar angle	Complete remission of RBD after surgery
	Jianhua et al. (2013) [65]	30 (M)	B cell lymphoma	Pontomesencephalic junction and upper/mid pons	Improvement of RBD after chemotherapy
Tumoral—paraneoplastic	Adams et al. (2011) [81]	55 (M)	Ma1 and Ma2 antibody-positive neurological disorder (squamous cell tonsillar carcinoma)		Not available
	Vale et al. (2016) [78]	66 (F)	Cerebellar degeneration (breast cancer)		Improvement of RBD after IVIG
		43 (F)	Cerebellar degeneration (breast cancer)		Remission of RBD after IVIG

Tumoral—Other	Shinno et al. (2010) [79]	76 (M)	Metastatic renal carcinoma	Not available	
		70 (M)	Stage IV gastric carcinoma with carcinomatous peritonitis	Not available	
		75 (W)	Gastric carcinoma	Not available	
Autoimmune	Iranzo et al. (2006) [20]	65 (M)	VGKC autoantibodies associated encephalitis	Bilateral mesial temporal lobe	Remission of RBD after IVIG and steroids
	Compta et al. (2006) [80]	69 (M)	Ma2 antibody-positive encephalitis	Bilateral amygdala and dorsolateral midbrain	No response after IVIG and steroids
Inflammatory—Demyelinating	Plazzi and Montagna (2002) [66]	25 (F)	Multiple sclerosis	Multiple cerebral periventricular, Pons	Improvement of RBD symptoms after ACTH treatment
	Tippmann-Peikert et al. (2006) [67]	51 (F)	Multiple sclerosis	Dorsal pons	Not available
	Gomez-Choco et al. (2007) [68]	49 (M)	Multiple sclerosis	Pons	Not available
Inflammatory—Others	Mathis et al. (2007) [69]	30 (M)	Acute parainfectious brain stem encephalitis	Medial and bilateral pontine tegmentum, ventral to the fourth ventricle	No response after steroid treatment
	Lin et al. (2009) [70]	46 (M)	Aseptic limbic encephalitis	Bilateral unci and medial temporal lobes	Not available
	St. Louis et al. (2014) [71]	47 (M)	Vasculitis	Dorsomedial pons	Not available
Postsurgical	Piette et al. (2007) [77]	56 (M)	DBS implantation surgery	Left subthalamic nucleus, substantia nigra	
Parasomnia overlap disorder					

(continued)

Table 12.2 (continued)

Etiology	Authors (year)	Age (sex)	Lesion type/diagnosis	Lesion location	RBD disappearance/ improvement after etiological therapy (if possible)
	Schenck et al. (1997) [75]	24 (M)	Post astrocytoma resection	Pons	Not available
		34 (M)	Multiple sclerosis	Not available	Not available
		50 (M)	Cerebral contusion	Not available	Not available
	Limousin et al. (2009) [76]	40 (F)	Acute inflammatory rhombencephalitis, myelitis, intracranial thrombophlebitis	Right pontine tegmentum and right dorsal medulla	Improvement of RBD after steroids
Status dissociatus					
	Provini et al. (2004) [73]	36 (M)	Post cavernoma resection	Ponto mesencephalic tegmentum	
	Condurso et al. (2006) [74]	62 (M)	Multilacunar state	Left basal ganglia and capsula, bilateral paratrigonal white matter, and median pons	Not available

Abbreviations: *IVIG* Intravenous immunoglobulin, *VGKC* Voltage-gated potassium channel, *DBS* Deep brain stimulation

[69–71] have been found in a few patients with RBD, as shown in Table 12.2. Moreover, lack of muscle atonia and disturbances of tonic-phasic REM sleep relationships were described in a case of an infiltrating tumor of the pons, before the formal identification of RBD in 1986 [72]. This topic is covered in detail in Chap. 9.

An acute status dissociatus (characterized by the complete NREM/REM sleep state boundary breakdown) has been described after surgical resection of a cavernoma [73] and in a multilacunar state [74].

In other cases RBD is part of parasomnia overlap disorder (POD), as described in different conditions including tumors [75] and inflammatory diseases [75, 76].

A nightly-recurring POD, secondary to a recurrent inflammatory disease of the brain stem and spinal cord of unknown origin, has been described in a 40-year-old woman with no prior parasomnia who developed an acute inflammatory rhombencephalitis with multiple cranial nerve palsies and cerebellar ataxia, followed by myelitis (6 months later), and by an intracranial thrombophlebitis (1 month after). Between and after these episodes, she presented severe RBD. During the episodes she talked, sang, and moved nightly while asleep and injured her son (co-sleeping with her) while asleep. In addition, she walked while asleep on a nightly basis. MRI revealed small hypointensities in the right pontine tegmentum and in the right dorsal medulla, documenting that a unilateral lesion is sufficient to enhance/release the axial and bilateral limb muscle tone and complex behaviors during REM sleep and also to trigger sleepwalking [76].

Finally, Piette et al. described a case of a 56-year-old parkinsonian patient who presented a unique episode of RBD beginning after the implantation of the exactly placed electrode for subthalamic stimulation. Immediately after the implantation of the left electrode (but not after a similar operation on the right side), the patient fell asleep and presented episodes of behavioral agitation or aggression during REM sleep. The authors suggested that a microlesion made by the electrode was responsible for triggering this parasomnia. Possible causes could be a lesion of the descending input from orexin neurons to the mesopontine region or the interruption of some descending inputs to the pontine REM sleep regulatory regions or, alternatively, a lesion in the substantia nigra might itself have been directly responsible for the emergence of the RBD [77].

12.4 Autoimmune Diseases

As discussed in greater detail in Chap. 8, RBD has been described in several rare paraneoplastic and autoimmune encephalopathies. Two patients with paraneoplastic cerebellar degeneration related to breast cancer presented with video-PSG confirmed RBD. RBD substantially improved after immunotherapy, raising the hypothesis that secondary RBD, at least in some cases, may be an immune-mediated sleep disorder [78]. In a few other cases, the relationship between the presence of advanced cancer and RBD was less evident and did not allow the possibility to discriminate whether the acute onset was of paraneoplastic or lesional origin or secondary to the effect of antitumor/palliative treatments [79].

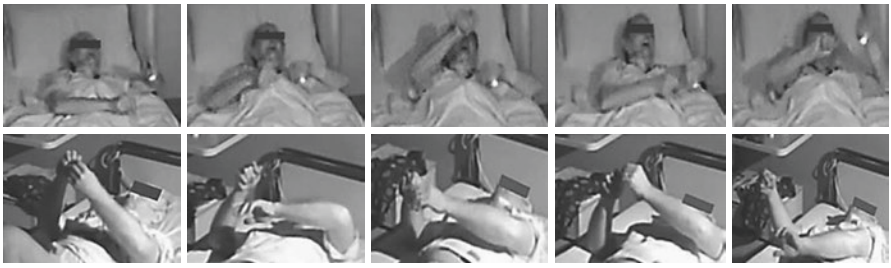

Fig. 12.2 Video recordings (selected frames) of oneiric stupor in two patients with Morvan's syndrome. Both patients perform the same gestures mimicking daily-life activities such as searching for objects

RBD is frequent in the setting of limbic encephalitis secondary to voltage-gated potassium channel (VGKC) antibody or anti-Ma1 and Ma2 antibodies [20, 80, 81]. In a series of six patients with non-paraneoplastic limbic encephalitis associated with antibodies to VGKC and RBD, immunosuppression resulted in the resolution of RBD in three patients, in parallel with remission of the limbic syndrome [20]. VGKC complex antibodies are associated also with Morvan's syndrome (MS), a disorder characterized by profound insomnia, dysautonomia, and peripheral neuromuscular irritability, sometimes associated with tumors such as malignant thymoma. In a case of paraneoplastic MS associated with antiVGK antibodies, 24-h PSG recordings documented a striking reduction in sleep spindles and in delta activity and the presence of autonomic and motor hyperactivity persisting throughout the 24-h [82]. As in DTs and FFI cases, this Morvan's patient presented with OS, and dream enactments mimicking daily-life activities (dressing, combing the hair, manipulating objects, etc.) coinciding with clusters of short REM sleep episodes, as shown in Fig. 12.2. The involvement of the thalamus and corticolimbic regions was shown in this case by serum immunoglobulin-G binding to neurons in these brain regions of the rat brain and by direct immunochemistry of frozen sections of the patient's brain tissues showing antibody leakage in the thalamus [82].

Transient RBD, improving as the disease resolves, has also been associated with Guillain–Barré syndrome, particularly in patients experiencing autonomic dysfunction and hallucinations [83].

12.5 Post-traumatic Stress Disorder (PTSD)

RBD can appear acutely after a stressful life event. In a cohort of 203 consecutive patients with iRBD, six patients (3%) were able to determine the date of onset of RBD because they associated it with a highly stressful situation (a robbery, a fraud, a cancer diagnosis) or a few days after a surgical procedure (a pacemaker implantation and cardiac bypass surgery in two patients) [84, 85]. At least four other cases of RBD triggered by major life stress have been published, involving a divorce, a frightening automobile accident without physical injury, a sea disaster, and public

humiliation, as reviewed [64]. The unresolved question in these ten cases was whether there was preexisting REM without atonia that predisposed these patients to develop rapid-onset RBD, since most people subjected to these stressful circumstances and medical procedures do not develop RBD [85].

RBD has been reported also in patients with prolonged PTSD, a disabling, chronic anxiety disorder resulting from exposure to life-threatening events, such as a serious accident, assault, abuse, or combat (DSM V) [86]. In one study of sleep muscle activity in a group of Vietnam combat veterans with current PTSD, an elevated percentage of REM sleep epochs with increased phasic twitching activity, as a presumed initial RBD-like sign in PTSD, was found [87]. Hefez et al. described two patients who were sea disaster survivors, and who had subsequently increased motor activity during REM sleep [88]. Schenck et al. reported an automobile accident survivor (without physical injury), who had nightmares reliving the accident and who presented with violent movements during sleep. His PSG showed increased phasic and tonic EMG during REM sleep [29].

Similarly increased EMG activity during REM sleep has been found in a unique series of 27 US veterans, 15 of whom also presented with PTSD [89]. More recently, Wallace et al. reported vPSG-confirmed RBD in four recent veterans of Operations Iraqi Freedom and Enduring Freedom, all of whom were taking SSRIs at the time of their PSG, although the time relation between SSRI initiation and RBD onset was not well clarified [90].

Furthermore, a novel parasomnia encompassing features of RBD (REM without atonia of variable degree) with nightmares and disruptive sleep behaviors has been proposed: "Trauma Associated Sleep Disorder (TSD)" [91, 92]. The authors described four young male soldiers, all with traumatic experiences (three involving combat and one involving divorce) heralding the onset of disruptive nocturnal behaviors and nightmares. All patients had RSWA and developed TSD from their traumatic experiences. According to the authors' suggestions, the term "Trauma Associated Sleep Disorder" (TSD) could describe a unique sleep disorder encompassing distinct clinical features, PSG findings, and treatment response to prazosin in patients with disruptive sleep behaviors, nightmares, and REM without atonia presenting after trauma.

12.6 Conclusions and Future Directions

Although our knowledge of acute RBD is based on a limited number of anecdotal, cross-sectional reports, literature data have documented that acute RBD is anything but rare [93, 94]. Acute RBD could have important implications for more fully understanding the underlying mechanisms of RBD, and, on the other hand, acute RBD can be of clinical value as a telltale sign. Sleep clinicians should be aware of the heterogeneous profile of RBD that can facilitate correctly diagnosing this parasomnia and enhance patient management and counseling. Physicians lacking special expertise in sleep medicine who are biased by the prevailing diagnostic perspective that links RBD with neurodegenerative diseases may fail to recognize cases

of incidental RBD. There are no published data on emergency department registry-based acute RBD incidence. Thus more awareness of the existence of these other forms of RBD and greater familiarity with the various potential clinical pictures may help to avoid misdiagnosis and inappropriate treatments. All patients who present with complaints of sleep-related behaviors and movements together with sleep talking and excessive dreaming should be screened for RBD, along with patients with neurologic or psychiatric disorders. Due to the possibility of iatrogenic RBD, a detailed medication history (including psychoactive medication and recently discontinued drugs) and stress-related social history should also be obtained [95]. Currently, studies that address treatment and long-term prognosis in antidepressant-associated or depression-associated RBD are lacking.

Among psychiatric patients, the association with RBD, although it can be mediated by antidepressant use, seems to involve a particular subgroup of patients, because it is present in more females, in younger patients, and with weaker association with neurodegenerative disease than previously described for RBD. If prospective studies confirm the existence of separate RBD subgroups (e.g., older men with neurodegenerative disease, younger patients with narcolepsy, and middle-aged women with autoimmune disease), further prospective studies will be necessary to determine whether these groups represent distinct pathophysiological mechanisms, how they manifest the same RBD phenotype, what the optimal treatments for these possible subgroups are, and what the prognostic differences across these subgroups are. This topic is covered in more detail in Chaps. 15 and 16.

Further research is necessary to clarify whether POD (RBD-NREM sleep overlap parasomnias) has a natural history different from that of typical RBD.

Finally, RBD should be clearly differentiated from OS or AE and more specifically DTs, FFI, and Morvan's syndrome. Despite the widely different etiologies and clinical courses, OS or AE is most likely to have a common pathogenetic mechanism different from disinhibition of the brain stem structures that control motor behavior during REM sleep found in RBD.

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Physiological Substrates of RBD Subtypes

13

Edgar Garcia-Rill and Carlos H. Schenck

13.1 Introduction

An understanding of the determinants of the main clinical RBD subtypes should include an understanding of the physiological substrates for these subtypes. These include the following:

1. Idiopathic RBD in adults, which in most cases represents an evolving alpha-synucleinopathy neurodegenerative disorder, as discussed in Chap. 4
2. Idiopathic RBD in children, a rare subtype that may represent a developmental anomaly manifesting as an incomplete or absent development of REM atonia, as discussed in Chap. 14
3. RBD associated with an established neurodegenerative disorder (Parkinson's disease/dementia with Lewy bodies/multiple system atrophy), as discussed in Chaps. 5 and 6
4. RBD associated with narcolepsy-cataplexy syndrome, as discussed in Chap. 11
5. Antidepressant medication-induced RBD, as discussed in Chap. 10

RBD associated with a broad spectrum of neurological disorders, and RBD as part of the parasomnia overlap disorder, will not be addressed in this chapter.

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13.2 Physiological Perspectives

13.2.1 Summary

During the last 10 years, two of the major discoveries made on the control of waking and sleep that have helped revolutionize our understanding of these two states will be addressed in regard to their relevance to RBD and its subtypes. This research was directed at the partly cholinergic pedunculopontine nucleus (PPN), the portion of the reticular activating system (RAS) that is active during waking and REM sleep, but less active during slow-wave sleep, and at its REM sleep-related target, the subcoeruleus nucleus dorsalis (SubCD) [1]. As such, the PPN modulates the manifestation of waking through ascending projections to the intralaminar thalamus, as well as the manifestation of REM sleep through descending projections to the SubCD [2]. We found that (1) these regions possess a proportion of cells that are electrically coupled through gap junctions, thus promoting coherence within each nucleus, and (2) every cell in these nuclei shows gamma-band activity that can export gamma frequency activity to its targets [3]. Neither mechanism has been studied extensively for its involvement in RBD or its subtypes. However, there is little doubt that research into these areas will permit a deeper understanding of RBD disease processes and point to novel directions for treating these disorders. These discoveries are described in detail in a recent book [4] and will only be described briefly herein, followed by some potential new directions in RBD research.

13.2.2 Neurological Substrates

The RAS is made up of the PPN, locus coeruleus (LC), and raphe nucleus, but the PPN is the most active during waking and REM sleep [5]. The LC and raphe nucleus both fire during waking and somewhat during slow-wave sleep, but not during REM sleep. The PPN is composed of different populations of cholinergic, glutamatergic, and GABAergic neurons [6]. The PPN contains three basic cell types based on in vitro intrinsic membrane properties [7–9]. Extracellular recordings of PPN neurons in vivo identified six categories of thalamic projecting PPN cells distinguished by their firing properties relative to ponto-geniculo-occipital (PGO) wave generation [10]. Some of these neurons had low rates of spontaneous firing (<10 Hz), but most had high rates of tonic firing in the beta/gamma range (20–80 Hz). PPN neurons increase firing during rapid eye movement (REM) sleep ("REM-on"), or both waking and REM sleep ("Wake/REM-on"), but decrease during slow-wave sleep (SWS) [5, 10–13], suggestive of increased excitation only during activated states. Stimulation of the PPN potentiated the appearance of fast (20–40 Hz) oscillations in the cortical EEG, outlasting stimulation by 10–20 s [14]. Injections of glutamate into the PPN increased waking and REM sleep [15], while injections of the glutamatergic receptor agonist *N*-methyl-D-aspartic acid (NMDA) increased only waking [16], and injections of the glutamatergic receptor agonist kainic acid increased only REM sleep [17].

REM sleep is distinguished from other states by low-amplitude, high-frequency EEG activity, muscle atonia, and PGO waves in humans and cats (P waves in the rat) [18, 19]**.** Nuclei located in the pons, including the SubCD, are critical for generation of this state [19–24]. The SubCD is most active during REM sleep [24, 25], and injection of the nonspecific cholinergic agonist carbachol or the glutamate receptor agonist kainic acid into this area induced a REM sleep-like state with muscle atonia and PGO waves [23, 24, 26–28]. Lesion of this area produced REM sleep without muscle atonia or P waves [19, 29–31]. The SubCD receives afferent input from several nuclei, including cholinergic, and perhaps glutamatergic, afferents from the PPN [32–35]. The SubCD projects to many areas, including the thalamus, hippocampus, pons, and medulla [36, 37]. The anatomic, cellular, and synaptic basis of REM sleep atonia has recently been further elucidated [38]. Furthermore, recent evidence has indicated that human RBD may be duplicated by inactivation of glutamate neurons in the rat SubCD, also named the sublaterodorsal tegmental nucleus [39].

13.2.3 Discovery of Electrical Coupling in the RAS

We discovered that some cells in the PPN and in the SubC were electrically coupled [40, 41]. We reported the presence of dye coupling and spikelets in some PPN and SubC neurons, as well as in the parafascicular nucleus (Pf), an ascending target of the PPN involved in thalamocortical oscillations [42]. We established the presence of electrical coupling using patch-clamp recordings of pairs of neurons and blocking action potentials with tetrodotoxin (TTX) and fast synaptic transmission with excitatory amino acid and GABA receptor blockers. In these conditions, intracellular pulses delivered to one cell induced a response in the other cell and vice versa, suggesting the presence of gap junctions in 7–10% of these neurons [40, 41]. We also determined that the neuronal gap junction protein connexin 36 (Cx36) was present in these regions and decreased in level along with the developmental decrease in REM sleep [40–42].

Modafinil is approved for treating excessive sleepiness in narcolepsy, sleepiness in obstructive sleep apnea, and shift work sleep disorder. Modafinil was found to increase electrical coupling between cortical interneurons, thalamic reticular neurons, and inferior olive neurons [43]. Following pharmacologic blockade of connexin permeability, modafinil restored electrotonic coupling. The effects of modafinil were counteracted by the gap junction blocker mefloquine. These authors proposed that modafinil may be acting in a wide variety of cerebral areas by increasing electrotonic coupling in such a way that the high input resistance typical of GABAergic neurons is reduced. We also found that modafinil decreased the resistance of PPN and SubCD neurons. The effects of modafinil were evident in the absence of changes in resting membrane potential or of changes in the amplitude of induced EPSCs and were blocked by low concentrations of the gap junction blocker mefloquine, also in the absence of changes in resting membrane potential or in the amplitude of induced EPSCs [40–42]. This suggests that these compounds do not act indirectly by affecting voltage-sensitive channels such as potassium channels, but rather modulate electrical coupling via gap junctions.

Gap junctions can be blocked through membrane fluidization such as that induced by the fast-acting anesthetics halothane and propofol [44, 45]. Oleamide promotes sleep and blocks gap junctions [46]. Anandamide enhances adenosine levels to induce sleep [47] and blocks gap junctions [44]. One possibility is that a mechanism by which these agents may induce sleep and/or anesthesia is through blockade of electrical coupling in the RAS. Carbenoxolone, a putative gap junction blocker, decreases the synchronicity of gamma oscillations [48], as well as seizure activity [49]. 18-glycyrrhetinic acid is a glycyrrhetinic acid derivative that blocks gap junctions [50]. Quinine and a related compound, mefloquine, also block gap junctions [51]. These considerations suggest that gap junction blockers induce sleep and gap junction promoters act as stimulants.

13.2.4 Discovery of Gamma-Band Activity in the RAS

A number of recent publications have described the mechanisms behind gamma-band activity in the PPN [2, 3, 52–55] and will not be reiterated. Briefly, these oscillations are mediated by voltage-dependent, high-threshold N- and P/Q-type calcium channels that are present in every PPN neuron, regardless of cell or transmitter type. These channels are distributed along the dendrites of PPN cells [56]. It has been shown that PPN neurons exhibit beta/gamma frequencies in vivo during active waking and REM sleep, but not during slow-wave sleep [10–13, 25]. Similarly, the presence of gamma-band activity has been confirmed in the cortical EEG of the cat in vivo when the animal is active [10, 14] and in the region of the PPN in humans during stepping, but not at rest [57]. A recent study showed that PPN neurons fired at low frequencies ~10 Hz at rest, but the same neurons increased firing to gamma-band frequencies when the animal woke up, or when the animal began walking on a treadmill [58]. That is, the same PPN cells were involved in both arousal and motor control. Thus, there is ample evidence for gamma-band activity during active waking and movement in the PPN in vitro, in vivo, and across species, including man.

However, gamma-band activity during waking has different mechanisms than gamma-band activity during REM sleep. Intracellularly, protein kinase C (PKC), which modulates kainic acid receptors (recall that kainic acid injected in the PPN induced REM sleep), enhances N-type channel activity and has no effect on P/Q-type channel function [59], but CaMKII, which modulates NMDA receptors (NMDA induced waking when injected into the PPN), was shown to modulate P/Q-type channel function [60]. That is, the two calcium channel subtypes in the PPN are modulated by different intracellular pathways, N-type by the cAMP/PK pathway and P/Q-type via the CaMKII pathway. Moreover, there are three cell types in the PPN, those bearing only N-type calcium channels, those with both N- and P/Q-type calcium channels, and those with only P/Q-type calcium channels [61, 62]. The implications from all of these results are that (a) there is a "waking" pathway mediated by CaMKII and P/Q-type channels and a "REM sleep" pathway mediated by cAMP/PK and N-type channels and (b) different PPN cells fire during waking (those with N + P/Q-type and only P/Q-type) vs. REM sleep (those with N + P/Q-type and only N-type) [61, 62] (Fig. 13.1).

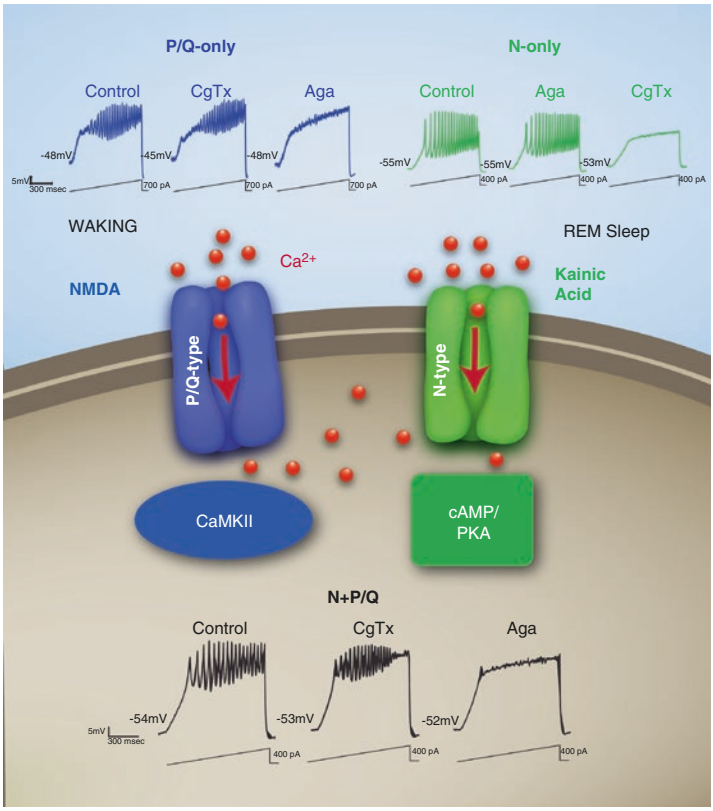

Fig. 13.1 Waking vs. REM sleep, differential control by high-threshold calcium channels modulated by separate intracellular pathways. *Top row*. Left records (blue) show that P/Q-only cells manifested ramp-induced oscillations (first recording) that were not affected by conotoxin (CgTX), an N-type channel blocker (middle recording), but were completely blocked by Aga (right recording), a P/Q-type channel blocker, i.e., this was a P/Q-only cell. Right records (green) show that N-only cells manifested ramp-induced oscillations (left recording) that were not affected by Aga (middle recording), but were completely blocked by CgTx (right recording), i.e., this was an N-only cell (Luster et al. 2015). *Middle row*. One of the intracellular pathways activated involves CaMKII (blue oval), which modulates P/Q-type calcium channels (blue channel), while the other pathway involves cAMP/PKA (green rectangle), which modulates N-type calcium channels (green channels). The CaMKII/P/Q-type pathway mediates beta-/gamma-band activity during waking, especially when activated by NMDA, while the cAMP/PKA/N-type pathway mediates beta-/gamma-band activity during REM sleep, especially during REM sleep (Luster et al. 2016). PPN cells with only P/Q-type calcium channels (20%) are assumed to be "Wake-on" and modulated by CaMKII (left side, blue channels). PPN cells with only N-type calcium channels (30%) are assumed to be "REM-on" and modulated by the cAMP/PKA pathway (right side, green channels). PPN cells with both N- and P/Q-type calcium channels (50%) are assumed to be "Wake/REM-on" and modulated by both CaMKII and cAMP/PKA metabolic pathways. P/Q-only and N + P/Q cells thus are expected to be active during waking, while N-only and N + P/Q cells are active during REM sleep [51]. *Bottom row*. Bottom records (black) show that N + P/Q cells manifested ramp-induced oscillations (left recording) that were only reduced by CgTx (middle recording) and were further reduced by agatoxin (Aga) (right recording), i.e., this was an N + P/Q cell (Luster et al. 2016, 2016)

Similarly, we showed that some neurons in the SubCD fired at frequencies above gamma-band (>100 Hz) at the beginning of a stimulus, but all SubCD neurons fired maximally at beta-/gamma-band following the initial portion of the current step [63]. However, unlike the PPN, voltage and sodium channel-dependent subthreshold oscillations appear to be involved in generating this activity in SubCD cells [63]. Subthreshold oscillations were isolated by blocking fast inhibitory and excitatory spontaneous synaptic activity. At membrane potentials below action potential threshold, subthreshold oscillations were observed and persisted at membrane potentials above action potential threshold. Subthreshold oscillations were also observed following inactivation of sodium channels underlying action potentials, suggesting the existence of two populations of voltage-gated sodium channels, one related to action potential generation and the other related to subthreshold oscillations [63].

A sodium-dependent mechanism was revealed using tetrodotoxin (TTX) , an extracellular sodium channel blocker, and QX-314, an intracellular sodium channel blocker. Low concentrations of TTX completely blocked action potential generation and reduced the power of gamma-band oscillations but did not abolish subthreshold oscillations, while high concentrations of TTX completely blocked the remaining subthreshold gamma oscillations. QX-314 in the intracellular recording solution blocked both action potentials and subthreshold gamma oscillations. These results suggest that beta/gamma frequency and sodium-dependent subthreshold oscillations underlie the gamma frequency firing of all SubCD neurons [63].

As far as the cortex is concerned, the difference between gamma-band activity during waking vs. REM sleep appears to be a lack of coherence [64]. That is, brainstem driving of gamma-band activity during waking carries with it coherence across distant cortical regions, while driving of gamma-band activity during REM sleep does not include coherence across distant regions [64, 65]. Also, carbachol-induced REM sleep with cataplexy is characterized by decreased gamma-band coherence in the cortex [66]. These results suggest that (a) brainstem centers drive gamma-band activity that is manifested in the cortical EEG; (b) during waking, brainstem-thalamic projections include coherence across regions; and (c) during REM sleep, which is controlled by the SubCD region (as described above, lesion of this region eliminates REM sleep, while injection of carbachol induces REM sleep signs), drives cortical EEG rhythms without coherence.

In summary, these findings showed that PPN gamma activity is mediated by high-threshold P/Q- and N-type calcium channels, while SubCD gamma is mediated by sodium-dependent subthreshold oscillations. We should note that both mechanisms are present in cortical cells to promote gamma-band firing, although, unlike PPN and SubCD, not every cortical cell has these intrinsic membrane properties. Moreover, gamma-band activity during waking (coherent) is different than that during REM sleep (noncoherent) and is modulated by different intracellular pathways (CaMKII vs. cAMP/PK, respectively) (Fig. 13.1).

13.2.5 Implications for RBD Subtypes

Normally, the transition between slow-wave sleep and REM sleep spans a few minutes as the frequency of PGO waves increases and muscle tone decreases [67]. That is, the REM sleep state is recruited rather than suddenly switched on. We presume that PPN neurons begin firing, especially those cell ensembles with N-type only and N + P/Q-type calcium channels, i.e., those involved in REM sleep drive [52]. Descending projections to SubCD, probably from both cholinergic and glutamatergic PPN neurons since both carbachol and kainic acid can induce REM sleep signs when injected into SubCD, begin activating the SubCD. We assume some coherence is provided by electrically coupled (especially GABAergic) PPN neurons. This brings the membrane potential of SubCD cells to levels sufficient to elicit subthreshold sodium-dependent which, combined with its electrically coupled neurons, begins to elicit PGO waves. But what happens to induce atonia in advance of the well-known hyperpolarization of spinal motoneurons [38, 68]?

The PPN has descending projections to medioventral medulla medium neurons that appear to participate in locomotor control, and to large reticulospinal neurons that can inhibit extensor muscle tone, similar to that seen during REM sleep atonia [69]. Some large cells in this region subserve the startle response [70], which is an automatic inhibition of extensor motor tone, and PPN lesions reduce prepulse inhibition of the startle response [71]. These results suggest that descending PPN projections to these large cells participate in modulation of startle response sensory gating. Such connectivity allows the PPN to modulate REM sleep atonia, the startle response, and fight-vs.-flight responses [4]. The SubCD, as described above, also sends projections to pontomedullary regions that give rise to reticulospinal neurons. Recent evidence has pointed to the glutamate neurons in the SubCD as playing a critical role in RBD [39], although the effects of neurodegenerative pathology of the SubCD for inducing REM sleep without atonia and clinical RBD suggest a more complex involvement of the SubCD and its inputs and outputs [72–74]. Disturbance of the SubCD (either lesional or pharmacologic from medication-induced RBD) thus appears to be the most likely site for the motor dysregulation of RBD.

The effects of the frontline treatment of RBD using the benzodiazepine clonazepam suggest that GABAergic output is potentiated by these agents to ameliorate the condition. Therefore, the role of electrical coupling in RBD, which generally decreases GABA output, would be involved only if there is excessive coupling, an unlikely event. On the other hand, we previously proposed that insomnia, or excessive waking, may be in part mediated by excessive expression of P/Q-type, waking-related calcium channels in the PPN [75]. Excessive expression of N-type calcium channels would be expected to increase REM sleep drive. Although it is not clear how this could lead to RBD, the fact remains that very little is known about gap junctions, high-threshold calcium channels, or sodium-dependent subthreshold oscillations in RBD.

The role of the PPN in Parkinson's disease (PD) has a long history. Suffice it to say that there are hundreds of patients worldwide who have been implanted with PPN deep brain stimulation (DBS) electrodes [52, 76–78]. PPN DBS has been

found to be effective in ameliorating gait, posture, cognitive function, and even sleep-wake cycles [52, 76]. Although there is no information available on the use of PPN DBS in patients who also suffer from RBD, i.e., RBD-PD, published studies of DBS of the subthalamic nucleus (STN) in PD have not been promising in regard to RBD. In one study, the presence of probable RBD in PD patients undergoing STN-DBS was associated with a less favorable outcome and a more prominent development of axial symptoms over time [79]. In another study, the incidence of clinical RBD increased after bilateral STN-DBS because de novo RBD developed and preexisting RBD persisted after DBS [80]. Nevertheless, future studies of DBS therapy in the PPN of PD-RBD patients should assess the impact of DBS on the severity of RBD.

The close relationship between narcolepsy-cataplexy (NC) and RBD (present in up to 60% of NC patients [81]) points to the involvement of the orexin/hypocretin neurons in the dorsolateral hypothalamus, which degenerate in narcolepsy. While many believe that hypothalamic orexin sites, as well as basal forebrain sites, drive waking, the fact is that they do so only through the RAS. For example, stimulation of these regions must be applied for much longer periods (10–20 s) [82, 83] compared to RAS stimulation (1–2 s) to induce waking [4, 82, 84]. In addition, optogenetic studies have found that induction of waking by stimulation of orexin neurons is blocked by inactivation of the LC in the RAS [82]. That is, the RAS may be the final output for the arousal induced by some of these modulatory regions [4]. Therefore, the co-expression of RBD with NC could well have its origin at the level of the RAS and not at such distant sites as the hypothalamus and basal forebrain.

Many narcoleptic patients also have hypnagogic hallucinations, a symptom that emphasizes the likely intrusion of REM sleep into the waking state. That is, both waking and REM sleep are dysregulated in narcolepsy. Almost all narcoleptic patients exhibit human leukocyte antigen (HLA) genotype expression for DQB1 [85], which is quite similar to the HLA expression (DQW1) we found in RBD patients [86]. About 80% of patients develop narcolepsy after puberty, similar to patients with schizophrenia, bipolar disorder, obsessive compulsive disorder, and panic attacks, unlike the usual late onset of RBD. Moreover, a series of studies on orexin knockout animals led to the conclusion that orexin was less related to arousal than to the levels of motor activity, perhaps mediated by its link to LC [87].

The literature on medication-induced RBD suggests that most classes of antidepressants, along with various other agents, can be triggers, as described above and discussed in Chap. 10. Bupropion, a dopaminergic/noradrenergic agent, has not been reported to induce RBD and is known to block gap junctions, at least in the heart [88]. In contrast, SSRIs, which do induce RBD in some patients, are also thought to act somewhat through gap junction blockade [89]. Therefore, these findings suggest that gap junctions are not involved in drug-induced RBD.

Finally, idiopathic RBD in children [90] appears to involve a lack of maturation of REM sleep atonia during the well-known developmental decrease in REM sleep [91]. We recently reported that the expression of N-type calcium channels in PPN decreases by ~350% during this period, while the expression of P/Q-type calcium

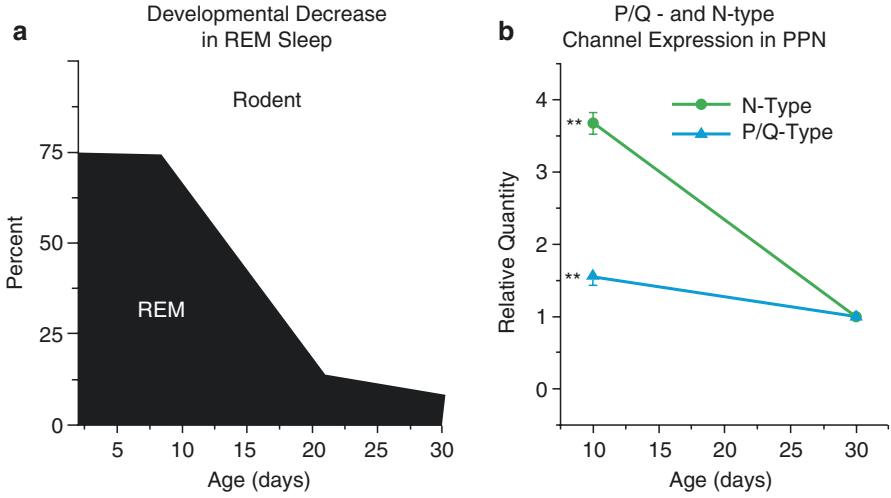

Fig. 13.2 Calcium channel expression during the developmental decrease in REM sleep. (**a**) Developmental decrease in REM sleep as a percent of sleep time. In the rodent, the decrease occurs between 10 and 30 days before assuming adult levels. (**b**) Relative quantity of N-type calcium channel (green line) and P/Q-type calcium channel (blue line) expression at 10 vs. 30 days in PPN punches from brain slices. N-type channel expression significantly decreased >350%, while P/Q--type channel expression decreased <35%. $^{**}p < 0.01$ [51]

channels decreases by a fraction of that number [92] (Fig. 13.2). These findings suggest that the developmental decrease in REM sleep may be due at least in part by a decrease in the expression of N-type channels in the PPN. The role of these channels in RBD, as stated above, has not been studied.

13.3 Conclusions and Future Directions

From the foregoing, it is evident that future research needs to address the roles of gap junctions and electrical coupling, as well as high-threshold calcium- and sodium-dependent intrinsic membrane oscillations, in RBD and its subtypes. The development of novel therapeutic, and perhaps preventive, strategies may depend on the examination of the development of REM sleep control and on the role of intracellular pathways modulating the manifestation of REM sleep vs. waking. The foregoing also strongly points to the SubCD, and perhaps also the LC, as a potential target for study. We provided preliminary evidence that the LC undergoes significant degeneration in RBD [93], but this finding needs to be confirmed. Nevertheless, the LC is known to inhibit the PPN [4], so that loss of LC neurons would tend to disinhibit waking and REM sleep drive. This may be one site of action of the benzodiazepine clonazepam in the amelioration of RBD.

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RBD in Childhood and Adolescence

14

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14.1 Introduction

REM sleep behavior disorder (RBD) is characterized by dream enactment, often with vocalization, during REM sleep in conjunction with the abnormal presence of chin and limb electromyogram activity, also termed REM sleep without atonia (RWA). The most common behaviors are kicking, yelling, or punching. RBD is typically observed in adults, but there are increasing reports of its occurrence in children and adolescents. Nevertheless, to date RBD has been reported in a small number of children. This chapter summarizes childhood-onset RBD with an emphasis on ontogenetic aspects and pathogenesis. The management and outcome are also likely different from those observed in adults and are also summarized herewith. The exact prevalence of RBD in childhood is not known. There are some similarities, along with differences, of RBD symptoms in childhood with nightmare disorder. The prevalence of nightmares that occur "always or often" is 2–11%, while nightmares that occur "now and then" show a prevalence of 15–31% [1].

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14.2 Perspectives from Sleep Ontogeny and Phylogeny

In the premature infant, between 30 and 32 weeks post conception, there is clear differentiation of sleep into active sleep and quiet sleep. Concurrent with brain maturation, there is also a progressive reduction in the percentage of REM sleep and an increase in the percentage of NREM sleep. By the time the infant reaches full term or 40 weeks post conception, the proportion of REM sleep has decreased to about 50% of total sleep time, with a corresponding increase in the non-REM sleep. By the time a child is 3–4 years of age, REM sleep decreases further to about 20–25% of total sleep time (i.e., the adult value), and the remainder of sleep is differentiated NREM sleep. Besides these two basic states of sleep, a third sleep state is also present in newborns. This is called "transitional sleep," which is most prevalent between 34 and 36 weeks post conception. The presence of transitional sleep has been well-recognized by early newborn sleep researchers [2]. They acknowledge that there are epochs of sleep in the newborn that cannot be clearly differentiated into active or quiet states because of a discordance between EEG activity and other polysomnographic (PSG) signs, viz., EMG and respiration. For instance, the low voltage irregular EEG pattern of active (REM) sleep may occur in conjunction with muscle twitches, tonic electromyographic activity, or regular respiration (both features of quiet and NREM sleep). This transitional or indeterminate sleep constitutes about 5% of total sleep in the near-term infant. It is composed of elements of both REM and NREM sleep [2]. The presence of motor activity such as twitches in REM sleep has been observed in rats as early as embryonic day 17 [3]. Sleep-related motor activity activates thalamocortical impulses, which facilitate columnar organization of the cerebral cortex [4]. The appearance of isolated RWA or RBD in later childhood might, therefore, represent regression to a primitive EEG-PSG pattern that resembles transitional sleep consequent to brainstem dysfunction in the region of the sublaterodorsal nucleus, as has been observed in adults with RBD [5]. Finally, the phylogenetic and ontogenetic perspectives have been discussed for how neuromotor disturbances beginning *in utero* and in early postnatal life may have a strong priming effect for the future emergence of RBD in adults, and childhood onset RBD (with predicted congenital cases) [6].

14.3 Pathogenesis

Some degree of motor activity in sleep is essential for survival, e.g., respiratory movements [7]. Preservation of muscle activity in sleep is also essential for neurodevelopment. For instance, in newborn mice, twitches of limb muscles in sleep lead to activation of volleys of thalamocortical electrophysiologic projections that facilitate columnar and laminar organization of the cerebral cortex [3, 4]. These studies underscore the critical role of motor activity observed in infant sleep for the purpose of brain development. *We propose that RWA and RBD represent persistence or reappearance of these infantile patterns of sleep in neurodevelopmental disorders such as autism or neurodegenerative disorders such as synucleinopathies.*

In this regard, the role of transitional sleep that is observed in healthy near-term infants needs careful consideration. One could postulate that transitional sleep of human infants is an evanescent state that resolves with progressive neuro-maturation.

In the presence of certain forms of brain dysfunction, such as synucleinopathies, or with neuropsychiatric conditions, such as autism, transitional sleep may reappear and be categorized as RWA (Fig. 14.1). At a neurophysiologic level, there is good resemblance between transitional sleep of newborn infants and RWA, with admixture of rapid eye movements, muscle twitches, and tonic electromyographic activity

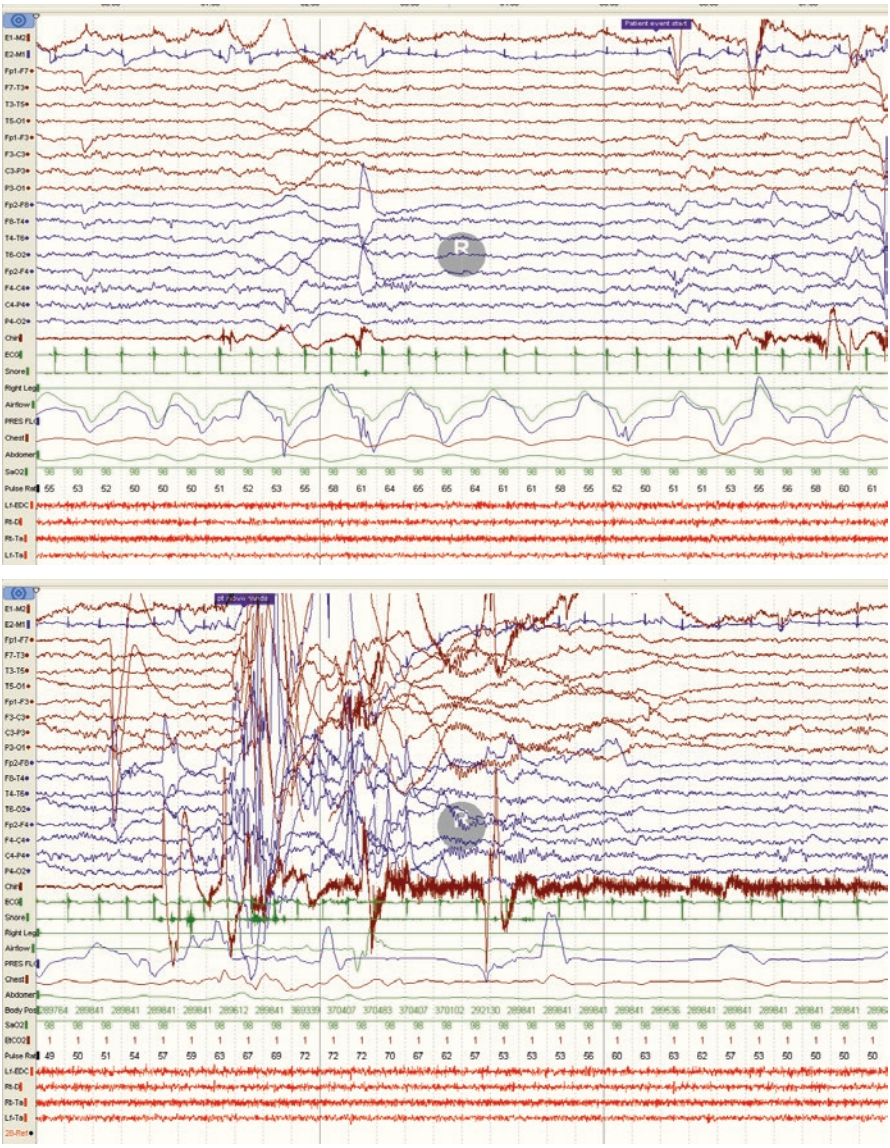

Fig. 14.1 Polysomnography recording (with multiple EMG channels and 16-channel EEG), during one event of a 17-year-old boy presenting with RBD mistaken to be epilepsy. Three consecutive epochs showing onset and offset during REM sleep, with high submental EMG tone and movement artifacts

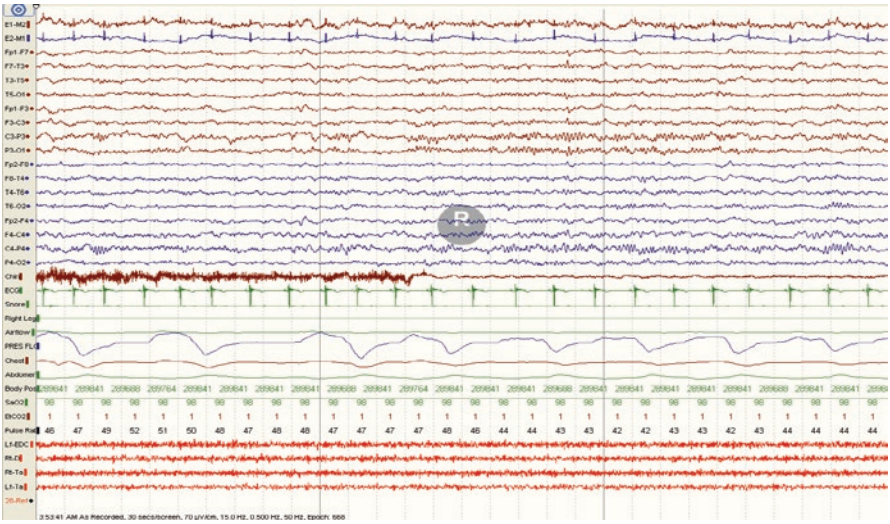

Fig. 14.1 (continued)

[8]. At a phylogenetic level, transitional sleep is perhaps analogous to the unihemispheric sleep of marine mammals such as bottlenose dolphins and fur seals which are obligated to maintain motor activity in sleep for homeostasis and in order to avoid predators.

The electrophysiologic basis of RWA and RBD is nicely explained in a recent review by Jennum et al. [9]. Authors have pointed out the reciprocal inhibitory relationship between pools of "REM off" and "REM on" neurons of the brainstem. Further, they point out that this inhibition is mediated via gamma amino butyric acid (GABA). The "REM off" system is composed of the ventrolateral periaqueductal gray matter (vLPAG) and the dorsal deep mesencephalic reticular nucleus (dDpMe). These neurons are active in wakefulness and during NREM sleep, but quiescent in REM sleep. The "REM off" neurons receive excitatory projections from hypocretinergic, noradrenergic, and serotonergic systems. The appearance of RWA in type 1 narcolepsy (characterized by hypocretin/orexin deficiency) may thus be explained as a consequence of insufficient activation of the "REM off" neurons, with inability to inhibit the pool of "REM on" neurons—this leads to increased muscle tone and activity, even in REM sleep. The "REM on" system is composed of the caudal laterodorsal tegmental nucleus and the sublaterodorsal nucleus. The "REM on" system serves to "inhibit the inhibitory" interneurons of the medullary reticular nucleus and lamina VIII of the spinal cord dorsal gray matter.

14.4 Clinical Presentation of REM Sleep Behavior Disorder in Children, Adolescents, and Young Adults

RBD has been recognized mainly as a disorder affecting elderly men, with the usual age of presentation being in the sixth or seventh decades, as per data from the initial three large series of RBD [10–12]. At the same time, in the first series by Schenck

and Mahowald, the earliest age of onset of RBD was 9 years [10]. Many individual case reports and a few case series of RBD in younger individuals have been published over the last several years [13–24].

14.4.1 Comorbidities/Etiology

Among the pediatric, adolescent or young adult population, a majority of patients appear to be suffering from RBD secondary to, or comorbid with, another neuropsychiatric condition and, hence, may present predominantly with clinical manifestations of the underlying condition rather than for the abnormal behavior during sleep [13–24]. Common examples of associations in this young RBD population would be the autism spectrum disorder (ASD) [16, 23], attention deficit hyperactivity disorder (ADHD) [23], narcolepsy type 1 [15, 21–24], Parkinson's disease with narcolepsy presenting at age of 18 years [24], and also medications such as serotonin-specific reuptake inhibitors (SSRIs) [25], or substance abuse (among adolescents and young adults). In the series by Lloyd et al., ten patients had coexisting ADHD [23]. Among 12 patients less than 25 years of age at presentation to our sleep disorders clinic at an Apex Academic Center in India, two had narcolepsy, type 1 two had epilepsy, one had narcotic drug addiction, and three had psychiatric disturbances. Two patients had been receiving an SSRI and patients with narcolepsy were receiving tricyclic antidepressant agents for their cataplexy (manuscript under review). Narcolepsy-RBD in childhood, and its unique clinical features, is further discussed in Chap. 11.

However, with one exception, most other reports on RBD among younger individuals also suggest RBD to either be clearly secondary to or be associated with various neuropsychiatric conditions (Table 14.1). The exception pertains to the parasomnia overlap disorder (POD), involving combined RBD and a NREM sleep parasomnia. In the initial series of 33 patients, the mean age at sleep medicine evaluation was 34 ± 14 (SD) years, with a mean age of POD onset of I5 ± 16 years (range 1–66 years), and 70% ($n = 23$) were males [26]. An idiopathic POD subgroup ($n = 22$) had a significantly earlier mean age of POD onset (9 ± 7 years) than a symptomatic subgroup (n = II) (27 ± 23 years, $p = 0.002$), although it should be noted that the mean age of onset of the symptomatic subgroup was in the young adult range. The ICSD-3 recognizes POD as a subtype of RBD [27]. Chapter 27 is devoted to the topic of POD.

A total of 40 patients with RBD and/or RSWA among the young have been reported to date, as shown in Table 14.1. In addition to these, another 10 patients from the series of Chiari malformations by Henriques-Filho PS et al. [19] could be added, given that the age range for the 23 patients with RBD recorded on PSG mentioned in that series was from 9 to 70 years, with 10 patients being children or adolescents.

14.4.2 Phenomenology

In an as-yet unpublished study, we evaluated the video-PSG studies of consecutive patients less than 25 years of age for RBD and/or RWA. One or more motor events

Table 14.1 Published case reports/case series of conditions associated with RBD and other characteristics of RBD and REM-Without-Atonia (RWA) in childhood or adolescence

Study type/reference	*N*	Associated condition	Clinical/PSG data
Case report Barros Ferreira et al. [13]	01	Infiltrating pontine tumor	Movements during REM sleep PSG: RWA during movements
Case report Schenck CH et al. [14]	01	After removal of mid-cerebellar astrocytoma	Movements during REM sleep on PSG
Case series Sheldon SH et al. [15]	05	One patient had narcolepsy; others characterized as idiopathic	Complex motor behavior associated with dreams Corresponding RWA (both phasic and tonic) on PSG
Prospective clinical and PSG study Thirumalai SS et al. [16]	11	Autism spectrum disorder	Clinical and PSG findings of RBD
Case reports Blaw ME et al. [17] Herman JH [18]	01 01	Hereditary quivering tongue with biting	Complex motor behavior; RWA on PSG
Case series Henriques-Filho PS et al. [19]	*10*	Chiari malformations	PSG evidence of RBD in 23/103 patients with Chiari malformations
Case report Trajanovic NN et al. [20]	01	Tourette's syndrome	Movements during REM sleep, flailing of the hands, and vocalization Corresponding RWA on PSG
Case reports Nevsimalova S et al. [21]	02	Narcolepsy-cataplexy	1st case: Harmful behavior and sleep-talking appeared. Attacked sister, with kicking and striking a wall repeatedly 2nd case: Sleep-talking and complex movements In both, motor events during REM sleep, with RWA on PSG
Case report Turner et al. [22]	01	Narcolepsy-cataplexy	
Case series Lloyd et al. [23]	15	Anxiety, ADHD, Smith-Magenis syndrome, pervasive developmental disorder, narcolepsy, idiopathic hypersomnia, and Moebius syndrome	RBD and RWA, documented on video-PSG
Case report Rye DB et al. [24]	01	Juvenile PD Narcolepsy Medication	RWA on PSG

ADHD Attention deficit hyperactivity disorder, *PD* Parkinson's disease, *RBD* rapid eye movement sleep behavior disorder, *RWA* REM sleep without atonia, *PSG* polysomnography

(violent jerky limb movements, rolling of limbs in bed, and crying) associated with RWA were recorded during the overnight studies of 50% of patients in the group of children with autism spectrum disorder (ASD) ($n = 16$), along with attention deficit hyperactivity disorder (ADHD) ($n = 10$). The recordings of patients in whom RBD was strongly suspected on their presentation in the sleep clinic ($n = 12$) showed more convincing "dream-enacting behaviors" in the events captured on videos corresponding to the periods of RWA (unpublished data).

As is evident from the series by Lloyd et al. [23], and similar observations made at our center, an academic tertiary care referral center in India, from 12 patients younger than 25 years, RBD in children, adolescents and young adults presents in a far more diverse manner as compared to the classical presentation with "dream-enacting behavior" in older adults, which is often violent. (The clinical presentation of RBD in adults under 50 years of age may represent an intermediate stage between the presentations of childhood/adolescent onset and older adult onset of RBD, as discussed in Chap. 15). The presenting symptoms reported can be flinging of limbs, rolling around, abrupt crying or yelling (mostly reported as associated with nightmares—"scary dreams"), and various nonspecific movements during sleep. More common causes of episodes of abnormal behavior during sleep in this young population include NREM parasomnias and seizures [28]. In fact, prior to the discovery of RBD, nightmares with dream-enacting behaviors were clumped together with nocturnal enuresis, sleep-walking, and sleep terrors, as disorders of arousal from slow wave sleep, rather than a REM sleep phenomenon [29]. While complex behaviors occurring in patients with somnambulism and confusional arousals can sometimes be included in the differential diagnosis of RBD, most NREM parasomnias such as sleep terrors are more restricted in their behavioral presentation. This topic has been previously reviewed [30]. The other important differential diagnosis in this age group is sleep-associated focal seizures with automatisms. It is, therefore, valuable to take into account important features in the history, especially the timing of occurrence, duration of episodes, and recall (Table 14.2).

14.4.3 Illustrative Case

A 17-year-old male high school student presented to the neurology outpatient clinic with a 3-year history of nightly episodes of mumbling with rolling of the eyeballs and purposive-appearing limb movements, while asleep, and very poorly responsive to treatment with antiepileptic drugs. His birth and developmental history were normal, and past history did not reveal any antecedents such as febrile seizures/status epilepticus, head trauma, or neuro-infections. He had a positive family history with an older brother aged 22 years and a paternal uncle aged 40 years also having nocturnal episodes, diagnosed as "epilepsy" and receiving oral phenytoin sodium as treatment without much response, but with less frequent episodes, occurring only

Table 14.2 Features differentiating RBD from seizures occurring during sleep

Characteristics of episodes	RBD	Sleep-related seizures (usually focal, with automatisms)	Points of caution
Timing of occurrence	Typically 1½ to 2 h after sleep onset; most often during the second half of nocturnal sleep. Generally confined to nocturnal sleep, not during daytime naps.	Any time during sleep, often within minutes of sleep onset. Sleep (nocturnal, diurnal).	RBD episodes can occur at sleep onset in patients with narcolepsy.
Duration of individual episodes	Variable, can last seconds to minutes. Can occur repetitively in close succession during the same REM sleep epoch and/or during multiple REM sleep epochs.	Variable, several seconds up to 3–4 min.	Status epilepticus can be long; however, evolution into rhythmic motor activity can often be observed.
Termination of episodes	Immediately when patient is woken up, or spontaneously at the end of a RBD episode.	Cannot be terminated through external stimuli.	Termination of seizures can be misattributed to external stimuli (to wake patient up), as seizures are often brief.
Phenomenology	Typically dream enactment in non-stereotyped, and often violent in adults; can be less complex, nonspecific and subtle among children. Phenomena differ from episode to episode, generally depending on dream content.	Can range from semi-purposive to bizarre and violent. Events in individual patients are mostly *stereotyped*.	
Recall	Patients can have recall of dreams during which episodes take place, at least in some episodes	No recall for any dreaming or abnormal behaviors, after most seizures	

once or twice a month. Clinical examination was normal, and a clinical diagnosis of possible autosomal dominant nocturnal frontal lobe epilepsy was made. Magnetic resonance imaging of the brain and a routine EEG were normal.

Overnight video-PSG with a (full) 16-channel EEG montage (Fig. 14.1) revealed 5 clinical events, recorded only during REM sleep, with non-stereotyped behavior (incomprehensible speech, grimacing, and flinging of limbs). The corresponding PSG findings fulfilled criteria of RWA (both tonic and phasic activity on chin EMG)

during all recorded episodes, and for almost 50% of 30 sec epochs of REM sleep during the night of recording.

With these data, and having ruled out epilepsy (through the recording of habitual nightly events on detailed video-PSG with 16 channel EEG recording), the MRI scan was reviewed again and was found to be normal. The patient was then reinterviewed for drug use history, and with much effort he shared a history of being dependent on multiple narcotic and prescription drugs (this patient reported use of cannabis, opium, dicyclomine, and tobacco, without informing us about dosage and frequency of use), similar to his brother and uncle.

The diagnosis of RBD was shared with patient and his brother and they were referred for de-addiction therapy. The uncle could not be contacted; hence, no follow-up was available for him. Antiepileptic medications were gradually tapered off. On follow-up at 6 months, both the patient and his brother were asymptomatic, without nocturnal symptoms, and were on no medications. The chemical dependency had been treated and resolved. Based on this course and response to intervention, it was presumed that the polydrug abuse possibly induced the RWA and RBD.

This case demonstrates how, in young patients presenting with episodic abnormal behavior only occurring during sleep, RBD has to be kept as a distinct possibility, and a detailed medication history as well as history for substance abuse must be elicited. In addition, a urine toxicology screen should be obtained, especially if the history is unreliable.

14.4.4 Diagnosis

The diagnosis of RBD in the pediatric and young adult population, as with the adult population, needs to be made in accordance with diagnostic criteria clearly detailed in the International Classification of Sleep Disorders, 3rd edition (ICSD-3) [27]. The essential features are repeated episodes of sleep-related vocalization and/or complex motor behaviors, the behaviors documented by video-polysomnography to occur during REM sleep or clearly presumed to occur during REM sleep based on clinical history, as well as demonstration of REM sleep without atonia (RSWA) on polysomnography. The diagnosis of RWA is made based on guidelines detailed in the American Association of Sleep Medicine scoring manual, version 2.3 [31].

While RWA is contained in the AASM scoring manual, there is no clear cutoff defined for the percentage of REM epochs recorded during the PSG study demonstrating RWA for the PSG diagnosis of RBD. Frauscher and colleagues recommended an evidence-based cutoff of 32% (of 3-second mini-epochs) for any sustained muscle activity/excessive transient muscle activity on mentalis EMG and ETMA on bilateral flexor digitorum superficialis muscles, *or* 27% of any EMG activity in the chin and/or phasic in the upper limb muscles [32]. These cutoff criteria were cited in the ICSD-3 diagnostic criteria for RBD.

As there are such few reports on RBD in the younger population, there are even fewer reports detailing their PSG characteristics. In our series, we found an average of 34% of REM mini-epochs showing RWA on the PSG studies of children and adolescents presenting to our clinic with RBD, in comparison to an average of 14–17% among children with autism and ADHD (unpublished data).

14.4.5 Management

Management of children and adolescents with RBD is largely similar to that in older adults. Lloyd et al. reported using oral clonazepam for 10 patients, melatonin for 2 patients, and discontinuation of an antidepressant medication in 1 patient among the 13 patients who were symptomatic for RBD, with excellent response in the majority [23].

Family members must be counseled regarding the potential of patients and/or bed partners to be injured from the RBD episodes, and so the need for adequate safety precautions around the bedside should be emphasized. Some safety measures could be the use of padded side rails in the beds of patients with RBD, placement of soft rugs on the bedside floor, the use of door alarms in the bedroom, and the use of other alarms in the bedroom that would be activated by high amplitude movement.

Since the majority in this age group have RBD secondary to other conditions, a thorough neurological evaluation—clinical as well as magnetic resonance imaging of the brain and cranio-vertebral junction—must be carried. A detailed neuropsychological assessment helps diagnose autism spectrum disorder and attention deficit hyperactivity disorder. In case of any suspicion of a genetic condition, especially in the case of a positive family history for systemic or neurological illness, a clinical geneticist should be consulted and further evaluation carried out. During the video-PSG, a 16-channel (or more extensive) EEG should be obtained to detect the diagnosis of epilepsy, for which accurate seizure and syndromic classification as well as establishment of etiology should be attempted, and appropriate antiepileptic medications should be initiated promptly. If the diagnosis of epilepsy is made, accurate syndromic classification and detailed investigation for the cause should be carried out. Initiation of appropriate antiepileptic medications should then be made immediately. In case of other sleep symptoms, such as excessive daytime somnolence and/or cataplexy, patients should be investigated for a diagnosis of narcolepsy, as cases have been reported in children with narcolepsy-cataplexy in whom the initial manifestation of disease was RBD that preceded the classical symptoms of type 1 narcolepsy [23]. A detailed medication history is essential, and adolescents and young adults must be taken into confidence, and a history of any substance abuse must be elicited, with a urine toxicology screen obtained, and efforts made to minimize use of any offending medication, such as an SSRI. This needs to be done in consultation with the treating physician. Certainly, any identified substance abuse disorder requires immediate and appropriate referral.

14.4.6 Prognosis and Future Directions

Since little follow-up data are available for childhood-onset RBD, and as patients may have an underlying neurodevelopmental disorder, questions regarding the course and prognosis of such patients remain unanswered. In addition, the association with neurodegenerative disorders is unknown. One reversible cause of RBD is the use of medications, such as antidepressants, which can promote the emergence of RBD [33]. However, in a prospective study of 27 older adult patients with idiopathic RBD (iRBD) taking antidepressant medications (mean age 64.1 ± 10.5 years), Postuma et al. found a significant increase in 12 out of 14 neurodegenerative markers tested, including olfactory loss and color vision discrimination dysfunction, in the 27 iRBD patients compared to 45 matched healthy controls [34]. However, the 5-year risk of progressing to a neurodegenerative disease, was significantly lower among those iRBD patients on antidepressants (22%) compared to iRBD patients in their series not using antidepressants (59%), indicating that antidepressant use in these patients unmasked an underlying neurodegenerative disease process without accelerating its clinical emergence [34]. It is currently unknown if antidepressant-associated RBD in children, adolescents, and younger adults would have similar findings. (Chapter 10 covers the topic of RBD associated with antidepressant medications and psychiatric disorders.)

The occurrence of RBD and RWA with autism and ADHD and potential associations with neurodegenerative illnesses is unclear but intriguing. The prevalence of PD has been reported to be higher in adults with autism compared to the general population [35, 36]. Mutations in the GPR37 gene associated with dopamine transport in PD have also been identified in patients with autism spectrum disorder [37]. In a systematic review, Schecklmann et al. suggested evidence for specific alterations of olfactory function, especially in disorders with dopaminergic pathology, such as ADHD and autism [38]. Some mutations in genes associated with PD have been shown to be associated with ADHD as well [39, 40]. There is, therefore, scope for systematic long-term follow-up studies involving RBD to explore these associations and for broadening the spectrum of knowledge on this interesting entity in younger patients.

A recent meta-analysis of genome-wide associations studies of restless legs syndrome (RLS) identified and replicated 13 new risk loci for RLS and confirmed previously identified 6 risk loci [41]. Of particular relevance to the topic of RBD and neurodevelopmental risk factors, in the RLS study just cited, gene prioritization, enrichment, and genetic correlation analyses showed that identified pathways were "related to neurodevelopment and highlighted genes linked to axon guidance (associated with SEMA6D), synapse formation (NTNG1), and neuronal specification (HOXB cluster family and MYT1)." Perhaps these neurodevelopment-related genetic findings in RLS are also present in RBD, another sleep-related motor disorder. (Chapter 41 covers the topic of the genetics of RBD.)

Finally, a major future direction for both clinical practice and research investigation related to childhood RBD in type 1 narcolepsy has recently been published

by the Bologna group [42]. In the first vPSG study to systematically analyze motor events during sleep in children with type 1 narcolepsy, 40 children (50% each gender), with mean age 12 years, and 22 controls were enrolled. Motor events were classified as elementary movements and complex behaviors, with complex behaviors in REM sleep being subdivided into "classic" RBD behaviors (brief, energetic) and "pantomime-like" behaviors (longer duration, with subcontinuous gesturing, mimicking daily life activities). Whereas both groups had elementary movements in sleep, only type 1 narcolepsy children had complex behaviors in REM sleep, as demonstrated by 32% (13/40) of patients, with 6 (15%) patients having "classic" RBD behaviors and 7 (17.5%) having "pantomime-like" RBD episodes that tended to recur in a stereotyped manner for several times nightly and at times approaching a continuous behavioral release in REM sleep (a form of "status RBD"). Furthermore, those type 1 narcolepsy patients with more severe motor-behavioral dyscontrol and increased RWA in REM sleep also had more severe daytime cataplexy. The authors concluded that for the first time a severe and peculiar motor-behavioral disorder in REM sleep was documented in pediatric type 1 narcolepsy and postulated that the linked findings with wakeful motor dyscontrol (e.g., more severe cataplexy) were manifestations of an acute imbalance in the hypocretin system. (The topic of RBD-narcolepsy type 1 is the focus of Chap. 11.)

In regard to narcolepsy, RWA, and RBD, a pertinent study has recently been published in which the presence of RWA and RBD were compared between pediatric patients with or without narcolepsy [43]. A major aim of the study was to determine if RWA is a valid objective diagnostic marker of narcolepsy. This was a retrospective cohort study of children aged 6–18 years who completed a nocturnal PSG and next-day Multiple Sleep Latency Test (MSLT). The study group included $n = 11$ with narcolepsy type 1 (NT1), $n = 6$ with narcolepsy type 2 (NT2), $n = 12$ with idiopathic hypersomnia (IH), and $n = 11$ with subjective hypersomnia (sHS). The RWA indices from the overnight PSGs (epochs of RWA/total stage R sleep epochs) across the groups were compared by using receiver operating curve (ROC) statistics. The median nocturnal RWA index of patients with NT1 was 15–30 times higher compared to sHS and IH (Ps < 0.005), but similar to that of the NT2 group ($P = 0.46$). RBD was notably present in 25% of patients with NT1 and NT2. In comparing those with and without narcolepsy, the nocturnal RWA index area under the ROC was 0.87 (0.6), 95% confidence interval (CI) = 0.75–0.99, $P < 0.001$. The threshold of having ≥1% of stage R sleep epochs with nocturnal RWA yielded a sensitivity of 88.2%, 95% CI = 63.6–98.5 and specificity of 60.9%, 95% CI = 38.5–80.3 for diagnosis of narcolepsy. In contrast, a threshold of ≥8% yielded a specificity of 95.7%, 95% CI = 78.1–99.9 and sensitivity of 52.9%, 95% CI = 27.8–77. Therefore, the nocturnal RWA index was found to be a very good diagnostic biomarker of pediatric narcolepsy. Depending on the clinical cutoffs utilized, this objective PSG marker can identify more children and adolescents with narcolepsy and reduce false-positive diagnostic results.

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RBD in Adults Under 50 Years Old

15

Yo-El S. Ju

15.1 Demographic Characteristics of Early-Onset RBD

From the earliest RBD cohorts, typical RBD patients have been described to be older (mean age 50s–60s) and male (~80% or greater) [1]. Even in cohorts of idiopathic RBD, in which there is no associated neurodegenerative disease, this demographic profile persists, with an average age of 58–68 years and male predominance (79–89%) [2–6]. Therefore, RBD occurring in younger adults is relatively rare and is termed "early-onset RBD," with the age of 50 years as a widely accepted but arbitrary cutoff. (RBD in children and adolescents is treated as a separate category, discussed in Chap. 14.) Four recent case series have described a higher proportion of early-onset RBD patients (26–43%) and have analyzed them separately from "late-onset" or typical RBD [7–10]. A highly consistent demographic feature of early-onset RBD is relative gender parity, in that the proportion of women is 41–48% [7–10]. Similarly, a cohort of probable RBD patients recruited from a younger (mean 42 years) outpatient psychiatric clinic population was 56% female [11]. Looking in the other direction, women with RBD tend to be younger, with a mean age of 48 years at RBD onset in a large meta-analysis [12], and in a 90-patient cohort comparing female to male RBD patients, the mean age of onset was 45 years compared to 50 years for men [13]. The possible reasons for relative gender parity in early-onset RBD include the association of RBD with antidepressants and depression (see next section), gender parity of narcolepsy (see section below), or potentially less referral bias related to clinical manifestations at a younger age. The interactions between gender and RBD are discussed in Chap. 16.

RBD is associated with neurodegenerative diseases, particularly synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy. However, secondary RBD due to neurodegenerative disease is

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much less common in early-onset RBD compared to late-onset RBD: 2.6% versus 29% [7], 9% versus 39% [9], and 9% versus 18% [10]. Even in patients with PD, probable RBD was significantly less prevalent in young-onset PD (age < 40 in 8%) compared to older-onset PD (25%) [14]. Rather, other causes of secondary RBD are more common in early-onset RBD, particularly antidepressant-associated RBD and narcolepsy (see next two sections). Otherwise, the proportion of idiopathic cases of early-onset RBD is 40–50%, on par with large RBD cohorts [1]. In the studies comparing early- and late-onset RBD, there was no clear difference in prevalence of idiopathic RBD: 51% versus 64% [7], 40% versus 31% [9], and 57% versus 78% [10]. To summarize, idiopathic RBD appears to be equally prevalent in early-onset RBD than in late-onset RBD, but the causes of secondary RBD are skewed in early-onset RBD away from neurodegenerative disease and toward antidepressants and narcolepsy.

15.2 Antidepressant Medications, Cataplexy, and Psychiatric Diseases

Years before RBD was described, treatment of cataplexy with antidepressants was noted to induce motor activity during REM sleep [15, 16]. Many subsequent investigations have established a strong association between antidepressants and RBD, both in the treatment of cataplexy and of psychiatric disorders (see Chap. 10). Antidepressant-associated RBD is more prevalent in early-onset RBD. In fact, the first case report of polysomnographically confirmed RBD induced by antidepressants was a 31-year-old man [17]. All four case series that separately assessed early-onset RBD identified a higher rate of antidepressant use in early-onset RBD compared to late-onset RBD: 58% versus 39% [9], 80% versus 46% [8], 7.7% versus 1.9% [7], and 17% versus 5% [10]. Indeed, higher rates of antidepressant-related RBD in women likely account for a large part of the gender parity in early-onset RBD.

The mechanism by which antidepressants induce RBD appears to be by causing REM sleep without atonia (RSWA). Polysomnography before and after initiation of sertraline in a young cohort (mean 33 years, 61% female) revealed increased RSWA posttreatment [18]. In a large, sleep-lab-based study of 10,746 patients (mean 53 years), the risk ratio of RSWA was 9.978 for those taking antidepressants compared to those who were not. This risk was not related to age, gender, presence of sleep-disordered breathing, or type of antidepressant [19]. RSWA appears to be specific to antidepressants, rather than related to depression [20], although this remains an open question that is discussed in Chap. 10. Additionally, while antidepressant-associated RBD comprises a relatively greater proportion of early-onset RBD, younger age is not a risk factor for having RSWA or RBD in response to antidepressants [21].

RSWA is not necessarily a benign polysomnographic finding. RSWA was associated with abnormal autonomic dysfunction in a young cohort (mean age 37 years) [22], and a longitudinal study of 14 patients with RSWA found 1 developed RBD

and 10 developed neurodegenerative biomarkers during follow-up, such as cognitive impairment, subtle motor slowing, impaired color vision, olfactory dysfunction, orthostatic hypotension, or substantia nigra hyperechogenicity [23]. However, since only a small proportion of people taking antidepressants develop RBD, additional vulnerabilities or triggers are likely necessary for RSWA to progress to full-blown RBD.

Some studies suggest psychiatric disease itself may act as a separate risk factor for RBD. For instance, in the large study mentioned above of 10,746 patients, antidepressants increased RSWA but did not increase the risk of RBD [19]. Another study found that patients with psychiatric disorder-related RBD had worse depression, anxiety, and increased nightmares compared to idiopathic RBD [24], suggesting that these psychiatric symptoms may increase RBD symptoms. A small study of ten patients (mean age 25 years, 50% female) with schizophrenia during their first "break" in a drug-naïve state showed increased RSWA compared to matched controls [25].

Life-threatening situations have been reported to trigger RBD-like symptoms or RSWA [26]. One small case series of RBD from a Veterans Administration Hospital found that 56% of patients with RBD also had post-traumatic stress disorder; this subgroup was fairly young (mean age 55 years, range 46–78 years) [27]. Another case series reported four young (age 22–39 years) male active-duty military personnel who had disruptive nocturnal behaviors and nightmares following traumatic events. All had RWSA on polysomnography, and all had clinical response in terms of both nightmares and nocturnal behaviors with prazosin. Based on clinical differences from typical RBD including a triggering traumatic event, prominent nightmares similar in content to the traumatic event, and response to prazosin, the authors suggested these cases constitute a separate disorder, named trauma-associated sleep disorder [28]. A matched cohort study of avalanche survivors in Iceland compared to people from unaffected towns assessed trauma-related symptoms 16 years later. Among those who were children (age 2–12 years) at that time, avalanche survivors reported significantly more acting out of dreams, while those who were adults (age 20–65 years) at that time reported significantly more nightmares related to the avalanche. While not confirmed by clinical sleep evaluation or polysomnography, these data suggest that age at exposure to trauma may modify subsequent nocturnal symptoms [29].

In summary, antidepressants or traumatic experiences may induce RSWA, and, in the setting of additional vulnerabilities, including possibly psychiatric diseases [11], they can trigger RBD, even in young adults.

15.3 Narcolepsy

Narcolepsy is the neurological disorder that most frequently causes secondary early-onset RBD. In the three studies that separately assessed causes of RBD by age, narcolepsy was a more common cause of RBD in early-onset compared to late-onset RBD: 39% versus 2% [7], 11% versus 9% [9], and 17% versus 0% [10]. The

first study assessing narcolepsy-associated RBD identified RBD in 10 of 17 patients, of whom 7 had early-onset RBD [30]. RSWA is common in narcolepsy, present in 75% of patients in a 100-patient cohort [31]. In narcolepsy with cataplexy, clinical symptoms of RBD are present in 45–61% of patients, with age of onset from childhood to early adulthood [32]. Of note, antidepressants, often used for treatment of cataplexy, increase the risk of RBD in narcolepsy [33]. In narcolepsy, RBD behaviors can occur during daytime naps (including MSLT naps) [30, 34] and occur with equal distribution in the first and second half of nocturnal sleep [35]. Narcolepsy-associated RBD is discussed in detail in Chap. 11.

15.4 Parasomnia Overlap Disorder

Parasomnia overlap disorder (POD) is characterized by both RBD and NREM parasomnias (see Chap. 27) and causes a disproportionately high proportion of early-onset RBD. POD was first described in a case series of 33 individuals who were young (mean 34 years). Age of onset of parasomnias was often in childhood, mean age 15 years, although there was a cluster of cases presenting in middle age [36]. Therefore, POD will be overrepresented in early-onset RBD, both middle-aged adults and patients with symptom onset during childhood being diagnosed in early adulthood.

Additional reports suggest POD may be a separate pathological entity from RBD, rather than a subclass of RBD. In a series of five patients with POD, all had symptoms beginning in their 20s and 30s, with four of them being diagnosed at age < 40 years. In all five patients, the NREM parasomnia was much more prominent, and RBD was discovered incidentally or was felt to be of minor clinical significance [37]. In another case, a woman with parasomnias starting at age 20 was diagnosed with NREM parasomnias only at age 53, but later RBD emerged at age 60 [38]. In another case, a 42-year-old man had a 7-year history of sexsomnia, somnambulism, sleep-related eating, and sleep talking; polysomnography revealed parasomnias out of N3 sleep as well as evidence of RBD. Notably, NREM parasomnia symptoms were much more prominent and were refractory to treatment of comorbid obstructive sleep apnea [39].

POD is relatively more common in early-onset RBD, and NREM parasomnias may predominate the clinical picture, especially early in the course; therefore the clinical history may not be typical for RBD.

15.5 Autoimmune Diseases

Autoimmune diseases may be associated with RBD, particularly in early-onset cases. In one cohort, 35% of women with early-onset RBD reported autoimmune comorbidities [9]. In a multicenter case-control study, corticosteroid usage was more frequent in RBD patients, but there was no significant association with autoimmune disease. However, the RBD cases were a mean 67 years of age, and analysis by early-onset RBD status was not performed [40].

Autoimmune or inflammatory diseases can cause direct injury to regions of the brainstem involved in REM sleep control and thereby cause lesional RBD (see next section). Additionally, there are reported cases of RBD occurring in inflammatory or autoimmune diseases without a clear brainstem lesion. Guillain-Barré syndrome (GBS), a postinfectious autoimmune disorder affecting motor nerves and variably central nervous system function, has been reported to cause acute RSWA and RBD, including one case of a 42-year-old woman [41]. In one of two cases of paraneoplastic cerebellar degeneration, one patient had RBD symptoms starting at 43, starting 3 years prior to cerebellar symptoms. The other patient was 66 years old, so it is uncertain whether this type of secondary RBD has particular predilection for early-onset RBD [42].

Other reported cases of RBD related to autoimmune or inflammatory brain diseases have all been late-onset cases, including VGKC antibody encephalitis (Morvan's syndrome) [43], IgLON5 antibodies [44], anti-Ma-associated syndromes [45–47], and anti-NMDAR antibody-associated encephalitis [48]. These and other autoimmune mechanisms are reviewed in Chap. 8.

15.6 Uncommon Causes of Secondary Early-Onset RBD

15.6.1 Lesional

Central nervous system lesions due to ischemic, demyelinating, neoplastic, inflammatory, or other etiologies can disrupt REM sleep control centers in the brainstem and subsequently cause RBD. Multiple sclerosis (MS) has been reported to present with RBD in one case of a 25-year-old woman [49] and to cause RBD in a 51-year-old woman [50]. Notably, in the former, RBD was initially diagnosed as idiopathic RBD, until additional neurological symptoms developed later, leading to a diagnosis of MS. In a large study of sleep disturbances in MS, 4 of 135 patients had RBD, of whom 3 were early-onset [51]. Strokes in the brainstem, compared to other brain regions, are associated with RBD [52]. While early-onset RBD may be caused by strokes, since age is a risk factor for stroke, stroke-associated lesional RBD is correspondingly rare in early-onset RBD. There are single case reports of early-onset RBD being caused by lymphoma at the pontomesencephalic junction [53], cavernoma in the floor of the fourth ventricle [54], acute inflammatory rhomboencephalitis [55], vasculitis in the dorsomedial pontine region [56], and inflammatory mediotegmental lesion [57]. Due to the diversity and scarcity of reports on lesional RBD, with the exception of multiple sclerosis, it is unknown whether lesional RBD is more common in early-onset cases (Chap. 9 comprehensively covers lesional RBD).

15.6.2 Wilson's Disease

Wilson's disease is a rare neurodegenerative autosomal recessive disorder due to abnormal copper accumulation and has protean manifestations, particularly at

presentation. In a case series of 41 patients with Wilson disease, RBD was present in five patients, and an additional sixth patient had a strong clinical history of prior RBD symptoms [58]. Age of onset was very young—by history, RBD symptoms began at mean 16 years (range 5–26 years), and age at RBD diagnosis was during early adulthood, with a mean age of 31 years. Three of the five patients had RBD prior to the onset of any other symptoms attributable to Wilson disease. History was typical in terms of RBD behaviors. Brain MRI demonstrated hyperintensities in the pontomesencephalic tegmental region [59]. Overall, while Wilson disease is rare, when associated with RBD, it seems to occur as early-onset RBD and in some cases as "idiopathic" RBD initially.

15.6.3 Ataxias

Disorders presenting with ataxia can be associated with RBD. Spinocerebellar ataxia type 3 (SCA3), or Machado-Joseph disease, is caused by a trinucleotide repeat in *ATXN3*. In a series of 15 consecutive patients with SCA3, 8 patients had a clinical history consistent with probable RBD at the time of the polysomnogram, and 3 additional patients developed RBD symptoms during 3-year follow-up. Age of RBD onset was a mean 42 years (range, 25–58 years) and occurred 6 years after ataxia onset. Of note, RSWA was elevated in all SCA3 patients regardless of RBD symptoms [60].

Non-hereditary ataxias presenting in adulthood include the cerebellar form of multiple system atrophy (MSA-C) and idiopathic adult-onset ataxia. In a case series of adult-onset ataxia, after follow-up for mean 9.2 ± 10.6 years, MSA-C was diagnosed in 24 of 50 (48%). Clinically probable RBD, present in 46% of patients, was correlated with a later diagnosis of MSA-C, with a positive predictive value of 87%. Age of ataxia onset was 54 ± 3 years for those who developed MSA-C, with RBD symptoms starting a mean 2 years later [61].

In summary, reported cases of RBD associated with ataxias, whether sporadic or hereditary, are in the upper age range of early-onset RBD, and RBD occurred after ataxia onset, although the reported cases were biased by recruiting from ataxia patient populations. If RBD occurs in the setting of a sporadic ataxia, there is a high chance that that patient will develop MSA-C.

15.6.4 Amyotrophic Lateral Sclerosis (ALS)

In a family with SOD1 mutation-related familial ALS, two siblings had violent dream enactment starting in their early 30s. Polysomnography confirmed RBD in one of the siblings, and could not be performed in the other. Interestingly, RBD began prior to onset of motor symptoms of ALS [62]. Additionally, the most common cause of familial ALS (and frontotemporal dementia), C9orf72 hexanucleotide expansion, was identified in 2 of 344 patients with RBD. Both patients had late-onset RBD (ages 58 and 65 years), one of them many years after PD

diagnosis [63]. No cases of early-onset RBD have been reported with ALS without a family history of ALS.

15.6.5 Beta-Blockers

In three reported cases, beta-blockers have been associated with RBD symptom onset. Bisoprolol was associated with typical RBD symptoms of disruptive parasomnias in one 50-year-old man starting at age 47 and one 56-year-old woman [64], and both RBD cases were confirmed by polysomnography. In both cases, symptoms fully resolved following discontinuation of bisoprolol. Notably, the latter patient had persistence of RSWA 2 months after discontinuing bisoprolol despite resolution of symptoms, suggesting that—similar to antidepressants—bisoprolol may unmask a latent predilection for RSWA and RBD. In a separate report of a 44-year-old man, violent parasomnias began 3 years earlier, around the same time as propranolol initiation for hypertension. Polysomnography revealed obstructive sleep apnea, and the case report does not comment on RSWA. Symptoms fully resolved with discontinuation of propranolol [65]. The small number of reported cases of beta-blocker-associated RBD, in contrast to the high prevalence of beta-blocker usage for treatment of hypertension and cardiac disease, with two of three of the cases being early-onset, suggests that secondary RBD due to beta-blockers may be more common in early-onset RBD.

15.7 Clinical Approach to Early-Onset RBD

15.7.1 Clinical Features

As discussed earlier, there is relative gender parity and high association with antidepressants and narcolepsy in early-onset RBD. Since women may have less violent behaviors than men [66], and narcolepsy-associated RBD is characterized by less violent behaviors [32], a relatively higher proportion of early-onset RBD patients will present for evaluation for reasons other than violent parasomnias. No difference has been found in injurious behaviors between antidepressant-associated RBD and typical RBD [24]. Furthermore, not all violent parasomnias in young adults are RBD. In a study of 13 young adults (mean age 29 years, range 19–58 years) with clinical histories of complex, violent, and clear-cut dream enactment behaviors very typical for RBD, only 1 patient had possible RSWA and none of the others had RBD on polysomnography [67]. Therefore, given the frequency of NREM parasomnias and POD in young adults, polysomnography is absolutely essential for the evaluation of suspected early-onset RBD.

Whether RBD is suspected initially or is discovered incidentally, clinical evaluation should attempt to identify a cause for RBD. A recommended approach to early-onset RBD is outlined in Table 15.1. Cognitive changes, motor abnormalities, and autonomic dysfunction should be assessed for as in typical RBD. Family

Table 15.1 Recommended clinical approach to early-onset RBD

Evaluation	Test or information	Reason
Clinical history	Psychiatric history, trauma exposure, and medication history Hypersomnia Cataplexy and other REM phenomena Parasomnias including during childhood that may be NREM parasomnias Autoimmune/inflammatory history Family history	Antidepressant- or beta-blocker-associated RBD, trauma-associated sleep disorder Narcolepsy Narcolepsy POD Autoimmune diseases ALS, SCA, Wilson's disease
Neurological examination	Brainstem signs Ataxia Corticospinal	Lesional RBD, autoimmune diseases SCA, MSA-C, Wilson's disease ALS, SCA
Sleep study	Video polysomnogram Full EEG Multiple sleep latency test	Confirm RBD, POD, NREM parasomnias Exclude seizures Narcolepsy
If no cause of RBD is identified or any abnormalities on neurological examination		
Blood	Ceruloplasmin Paraneoplastic panel	Wilson's disease Autoimmune diseases
Imaging	Brain MRI	Lesional RBD, Wilson's disease
Spinal fluid	Oligoclonal bands Paraneoplastic panel and other autoantibodies	Multiple sclerosis Autoimmune diseases

Note: refer to text for the meaning of the abbreviations

history of RBD type of behaviors should be queried, although a study found that there was no difference in age of RBD onset in those with and without family histories (55 versus 57 years) [68]. Family history of sleep disorders and neurologic disorders (such as ALS or SCA) should be sought. Neurological examination, in addition to evaluating cognitive, motor, and autonomic functions as in typical RBD, should assess for ataxia, corticospinal signs, and brainstem pathology such as cranial nerve deficits, to address less common causes of secondary RBD.

Video-polysomnography is necessary for the diagnosis of RBD. In cases of suspected early-onset RBD, due to the prevalence of POD in this population, careful evaluation should be performed for non-REM parasomnias in addition to RBD. A multiple sleep latency test is strongly suggested to evaluate for narcolepsy, as well as to evaluate for RSWA and RBD during naps. In terms of RSWA, while one study had shown increased EMG activity and movements during REM sleep in children and those >65 years age, compared with young-middle-aged adults [69], another study with strict selection for healthy sleepers showed no age- or sex-related correlations with REM sleep muscle activity [70]. In RBD patients, both increased age and male sex are associated with elevated RSWA by manual scoring [71], but not by an automated RSWA scoring method [72]. Therefore, given the gender parity and younger age of early-onset RBD, RSWA may be less prominent compared to typical RBD; however, there are no differences in scoring criteria by age.

If a polysomnogram confirms RBD and no cause can be identified, additional evaluation is recommended. Brain imaging should be performed if there are any abnormalities on neurological exam, and ideally in all cases of idiopathic early-onset RBD. Laboratory tests to screen for Wilson disease and autoimmune syndromes are recommended. If there is any suspicion for MS or autoimmune disorders, lumbar puncture should be performed to obtain cerebrospinal fluid for further testing. As in typical idiopathic RBD, long-term follow-up is essential to assess for the development of neurodegenerative disease, as well as rarer neurological syndromes associated with RBD.

15.7.2 Treatment

There are no studies specifically assessing treatments for early-onset RBD; however, there are additional considerations for differences in treatment approach. Since antidepressant-associated RBD is so common in early-onset RBD, discontinuing antidepressants or changing to an antidepressant not known to trigger RBD (e.g., bupropion) may be helpful, although collaboration with the physician prescribing the antidepressant is essential. Notably, while discontinuing the offending antidepressant reduces the frequency and severity of nocturnal behaviors, RSWA may not remit; a small study assessing the effect of changing antidepressants showed no improvement in RSWA after mean 13 months (range 9–19 months) [73]. Narcolepsy-associated RBD may be triggered or worsened by antidepressants used for cataplexy. If a cause of RBD can be identified, for instance, multiple sclerosis, autoimmune syndrome, or Wilson's disease, treatment of the underlying condition may decrease RBD symptoms. Safety precautions are especially important with the higher frequency of POD in early-onset RBD, in which the risk of patients leaving the bedroom or engaging in complex behavior is higher than for typical RBD. In a study assessing injury in RBD, younger age was associated with more frequent episodes of dream enactment [74]. Overall, exceptional care must be taken to secure the sleeping environment. Otherwise, the mainstays of RBD symptomatic treatment are clonazepam and melatonin, as in typical RBD.

15.7.3 Prognosis and Conclusions

Despite the large and growing literature on the risk of developing neurodegenerative disease in idiopathic RBD and potential prognostic factors, the neurodegenerative prognosis for early-onset RBD is unknown. An extensive review of the literature on signs of neurodegeneration in idiopathic RBD identified only one study where the [mean ± one standard deviation] age of participants included <50 years. In a small case-control study assessing skin punch biopsies, the intraepidermal nerve fiber density was reduced in RBD compared to controls, with RBD group aged range 22–71 years, mean 54 ± 15 years [75]. Also, as discussed above, RSWA was associated with abnormal autonomic dysfunction in a young cohort (mean 37 years) [22].

Single and multicenter studies have demonstrated that increased age is a risk factor for development of synucleinopathy in RBD patients [76, 77]. However, the number of early-onset cases in these studies is too low, and follow-up has not been long enough (for young adults to reach typical age for neurodegenerative diseases) to draw firm conclusions about neurodegenerative risk. The risk of Parkinson's disease in individuals with idiopathic RBD aged 50–54 years is ~25% [78]; therefore the risk is <25% in early-onset RBD. Antidepressant-associated RBD has a lower risk of conversion to neurodegenerative disease than non-antidepressant-associated RBD; however there are subtle markers of neurodegeneration and some progression to synucleinopathy in people with antidepressant-associated RBD [79]. In a convenience sample of 27 RBD patients who remained idiopathic RBD for at least 15 years but eventually developed a neurodegenerative disease, age of RBD symptom onset was young (range 21–60 years, median 49 years). Neurodegenerative symptoms began, on average, 25 years later, and the distribution of neurodegenerative diagnoses—13 with PD, 13 with cognitive decline, and 1 with multiple system atrophy—was similar to typical RBD. Autonomic symptoms were common, present in 74% of patients [80]. Overall, there are insufficient data to determine neurodegeneration risk in early-onset idiopathic RBD, but subtle signs of neurodegeneration in small cohorts suggest this risk is higher than in the general population. Close clinical follow-up is therefore recommended for early-onset RBD patients.

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RBD: Gender Implications

16

Cynthia L. Bodkin

16.1 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) has historically been reported more frequently in men, starting with the first report of the disorder which identified four men and one woman [1]. This brings considerable inquiries specific to gender differences and their implications. RBD is associated with many neurologic disorders including narcolepsy and neurodegenerative disorders. Idiopathic RBD (iRBD) was thought to be a disorder unrelated to other neurological disorders or clinical syndromes. However, recent evidence supports that iRBD can be one of the early manifestations of a neurodegenerative disorder (Chaps. 4 and 36). As medical research continues to advance in the field of neurodegeneration, and as disease-modifying agents become a reality (Chap. 44), a better understanding of gender differences has treatment consequences. This chapter will discuss gender in RBD and the clinical and research implications.

16.2 Gender Prevalence

iRBD has been reported to be notably male predominant, with the reported range extending up to 90% male [2, 3]. However, more recent studies either fail to demonstrate statistical gender differences [4, 5] or demonstrate overall male to female ratio of RBD closer to 2:1 [6, 7] compared to older series ranging 5:1–8:1 [8–13]. The discrepancy between recent studies compared to older series may relate to increased awareness about RBD, the higher volume of younger patients included in recent studies and/or increased access to video-polysomnography (vPSG). vPSG

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can help diagnose unrecognized RBD, as only 30–40% of patients with RBD in one study had a chief complaint suggestive of RBD [5].

16.2.1 Gender Differences of RBD Among Synucleinopathies

There is a strong association between synucleinopathies and RBD, with the most common synucleinopathy being Parkinson's disease (PD), which has a 1:5 male to female ratio in western populations [14]. Gender distribution of RBD or probable RBD (pRBD) in PD has recently demonstrated a closer balance with 31–40% women and 43–49% men [15–17]. A cross-sectional evaluation of patients with idiopathic PD demonstrated higher phasic electromyographic metric (PEM) in men compared to women in NREM and REM sleep despite no difference in dream enactment behavior [18]. However another study with RBD failed to demonstrate differences in EMG activity during REM sleep regardless of women having fewer behaviors [19]. Interestingly, a gender difference is not seen in multiple system atrophy (MSA) where almost all patients have RBD [3]. In patients with PD, women with pRBD tend to be older, with a shorter duration of PD symptoms, with higher levels of anxiety and depression, and with more sleep disturbances and decreased hours of sleep [20].

16.2.2 Gender Differences of RBD Among Other Disorders

Outside of the synucleinopathies, there is less male predominance with RBD in neurological disorders. Similar gender frequencies are seen in narcolepsy and multiple sclerosis [21]. RBD was reported in 12% (5/34) of patients with Wilson's disease, 4 of them being women [22], in contrast to the higher prevalence of Wilson's disease in men [23].

Autoimmune disorders and paraneoplastic disorders have also been linked to RBD. RBD has been reported with paraneoplastic cerebellar syndrome. Both cases were women with breast cancer and negative paraneoplastic antibodies [24]. Limbic encephalitis with potassium channel antibody has been associated with RBD; however all six cases were men [25].

16.2.3 Gender Differences of RBD with Age and Type of Disorders

Gender differences vary by age. Compared to women in the older age groups, women had a higher rate of RBD in early-onset RBD (before age 50 years), with a range of 41–45% compared to late-onset RBD of 11–25% [6, 7, 26]. Early-onset RBD had a higher rate of psychiatric diagnosis, antidepressant use, autoimmune disease, and narcolepsy, with neurodegenerative disease reported less often (2.6% compared to about 18% overall) [6, 7, 19, 26]. The high rate of autoimmune disease among female patients could account for the higher percentage of RBD in women

under age 50 [6]. Referral bias may also play a role given that psychiatric and rheumatologic patients frequently have fatigue and tiredness, which are common indications for referrals to sleep centers and sleep studies.

16.3 Gender Differences in RBD Dreams

Gender differences in dreaming are noted among patients with PD. Males with PD had more dreams involving aggression, work, adventure, and sports compared to women who had more dreams about family, friends, and daily activities [27]. However, when comparing patients with RBD or pRBD and PD, gender differences were not always noted [19, 27] or investigated [28]. A small reported series found that women had more victim dreams with no violent behaviors [29]. In patients with PD and pRBD, the women were all able to recall dreams, with content of being chased with 40% flight response, 40% fight response, and 20% with both responses [20]. Aggression and violence were significantly higher among RBD-PD men than with non-RBD-PD men. RBD patients' dreams were described as more often being chased, being defensive, or being aggressive and did not reflect daily life [27].

16.4 Gender Differences in RBD Behaviors

Gender differences in RBD behaviors are theorized to contribute to reporting bias, with men having more aggressive and violent behaviors. When comparing RBD behaviors in patients with Parkinson's disease, both men and women have vocalization, with men having more violent behaviors and women reporting more sleep disturbances, flailed arms, a tendency to use upper limbs, and run more than men [15, 20, 27]. One study demonstrated that only men had sleep-related injuries in patients with RBD and Parkinson's disease [30]. This male predominance with violent behaviors is seen with other disorders associated with RBD [22, 31]. Females have also been reported to have fewer RBD behaviors on vPSG [19, 32]. Higher muscle activity in REM sleep in the legs was found in men with RBD compared to higher muscle activity in REM sleep in the arms of women with RBD, in one study [29]. However, in a Chinese population study, no differences among behavioral symptoms or violence between men and women with RBD were noted, although 82% were men in that study [12].

Gender nonconformity (transsexual status) was mentioned in a study on the different manifestations of RBD in men and women [29]. One patient was transsexual, was born a male (with gender change surgery 13 years prior to vPSG), had arm movements in REM sleep that were much less than that usually found in women, and did not differ substantially from those of men. This particular patient was the only woman in the case series with violent behaviors associated with RBD. Dream content was not mentioned, which raises the question of whether dream content and/or behaviors would be more consistent with their gender at birth or with the gender identity (resulting in transsexual surgery). The abovementioned case appears

to be more consistent with birth gender. One unreported homosexual iRBD female identified herself as female but labeled herself as a "tomboy" (CL Bodkin, unpublished observation). She described dreams where she was protecting people and/or animals from an attacker. She herself was neither the victim nor the attacker, but the dreams and behaviors were violent to protect her loved ones. Therefore, questions regarding gender nonconformity should be included in future studies looking at gender differences in RBD.

16.5 Etiology of Gender Differences in RBD

Hormonal factors, other predisposition factors, referral bias, and decreased sensitivity of detecting RBD in woman from vPSGs may contribute to the reported male predominance of RBD. Testosterone is one hormone that has been implicated. However when comparing men with PD-RBD to men with PD-non-RBD, there was no difference in testosterone levels [33]. Estradiol has been proposed to be protective specifically in glutamate-induced toxicity in vitro [34]. Estrogen has been shown to have effects in the central nervous system with respect to serotonin, norepinephrine (NE), and dopamine [35]. It has been suggested that higher estrogen levels in women may lower NE neurotransmission leading to reduced phasic REM activity, based on a study in anesthetized rats [36]. However, there is a lack of evidence that estradiol or other sex hormones differ in male patients with or without RBD [33, 37]. Although the evidence argues against hormone status as a risk factor for RBD, it does not rule out a hormonal role in phenotypic differences between men and women, or violent vs. nonviolent behaviors, in RBD.

Men may be preferentially predisposed to RBD. When looking at REM sleep without atonia (RSWA) in a retrospective study in patients who underwent PSG evaluations, men had higher phasic muscle activity in the leg compared to women [38]. Undiagnosed neurodegenerative diseases in men could explain some of this difference. When looking at small movements during NREM and REM sleep in a prospective study with healthy volunteers, women were found to have shorter duration of movements, and men had greater movement indices in the upper and lower extremities [39]. These findings suggest underlying gender differences with baseline sleep motor dyscontrol, which may place men at higher risk for RBD.

Given the strong relationship between RBD and neurodegenerative diseases, such as PD, the high rate of male RBD patients could in part be explained by the higher male incidence of PD. Male to female incidence of PD is estimated to be 1.5 with a male to female difference more evident in western populations and not demonstrated in Asian populations. The lack of gender difference in Asian populations also suggests genetics rather than hormonal factors, such as estradiol, in playing a role in the risk for PD [14].

Referral bias likely plays a partial role in gender incidences. Women, on average, live longer than men and therefore may not have a bed partner. This is supported by reports that men with RBD are more likely to have a bed partner [31]. If behaviors are less violent and women are not suffering injuries, and they are sleeping alone

(and unaware of their sleep behaviors and without a spouse who could complain of excessive movements during sleep), then they may be less likely to seek medical attention. The possibility of vPSG being less sensitive in women, especially if arm EMG electrodes are not used, could contribute to the underdiagnosis of RBD in women. The higher ratio of women in recent studies suggests a greater awareness of women with RBD. Only 10.4% of reported RBD patients between 1990 and 2003 were women, while 23.2% of reported RBD patients were women between 2004 and 2014 [31].

16.6 Gender Implications in RBD

It is important to recognize RBD in both men and women, for compelling reasons. In one study of 93 patients with iRBD, the 12-year risk for developing a neurodegenerative disease, from the time of iRBD diagnosis, was 52.4%, and the risk of progressing to a neurodegenerative disease was similar in men and women [2]. Also, more recent findings from a cohort of 174 iRBD patients at another center found the risk of a defined neurodegenerative disorder from the time of iRBD diagnosis to be 33% at 5 years, 76% at 10 years, and 91% at 14 years, with the median conversion time being 7.5 years [40].

Although currently there are no disease-modifying agents, clinical trials in this area are being developed. As disease-modifying agents become a reality, early recognition of RBD will be of upmost importance. Healthcare providers across a wide range of specialties will need to be made aware of RBD and its strong link with parkinsonian neurodegenerative disorders in both women and men and be mindful of the gender differences in RBD and their different clinical profiles. The recent trend toward home sleep testing (HST), which is not indicated for nor sensitive in diagnosing RBD, could greatly underdiagnose RBD. In two reports, only 30–40% of patients with RBD had presented to a sleep center with a chief complaint suggestive of RBD [5, 6]. Therefore, healthcare providers need to carry out a detailed sleep evaluation prior to and/or after HST, as well as after treatment of any diagnosed sleep disorder breathing.

Besides the risk of developing a neurodegenerative disorder, there are social and physical implications to the bed partner. Women and children can be victims of violent RBD behaviors, which can include choking, headlocks, and punching [41]. This often leads to spouses sleeping in a different bed and/or room. Despite spouses often being victims of repeated injuries from RBD behaviors, necessitating sleeping in a different room, only two cases with divorces related to RBD have been reported [42, 43]. This most likely reflects how the majority of RBD reported cases involve older men who have been married for decades, and so their spouses understand that the sleep violence is completely out of character from the waking personality.

RBD is a treatable and important disorder to recognize, given the risk of future neurodegenerative disorder and the psychosocial implications. Some women and men may have similar presentations. However, women may present with less violent dreams and behaviors, have less tonic and phasic EMG activity during REM

sleep and less behavioral abnormalities during REM sleep, and also have a chief complaint with symptoms other than a parasomnia. A detailed history and the use of a screening questionnaire are important for both genders and should include an assessment of any impact to the bed partner and the relationship, if appropriate. Management should also include monitoring for resolution of all sleep symptoms in the setting of comorbid sleep disorder.

Note Added in Proof: Equal RBD gender ratio was recently found in the first general population-based study of PSG-confirmed RBD (in contrast to male gender predominance in RBD patients presenting to sleep clinics): Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and determinants of REM sleep behavior disorder in the general population. Sleep 2017; doi: 10.1093/sleep/zsx197.

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RBD: A Window into the Dreaming Process

17

Isabelle Arnulf

17.1 Introduction

Rapid eye movement sleep behavior disorder (RBD) is often defined as dream-enacting behaviors. However, more attention has been paid to the motor aspects (because of risk of injuries) and to RBD as a preclinical sign of neurodegeneration than to its dreaming aspects. Notably, the first RBD animal model, developed in cats as early as in the 1960s by the Jouvet group in Lyon, France, was named "oneiric behavior," because these animals displayed apparent dream-related behaviors (leaping, chasing, and fighting) during REM sleep [1]. Note that "oneiric" is the Greek-origin term designating dream aspects. The model was even used to determine "what does a cat dream about?" illustrating how much these pioneers believed in the dream-action hypothesis [2, 3].

We would like to develop here in depth the dreaming aspects of RBD and what insight RBD has brought to the domain of cognition during sleep. RBD constitutes a unique window to study the dreaming process from a point of view external to the dreamer. Indeed, behaviors, facial expressions, and verbal utterances are in accordance with the dream reports obtained upon awakening. This condition (named isomorphism) brings strong, unbiased evidence that dreaming occurs during sleep and is not built upon awakening or reconstructed afterward by the sleeper to please the investigator/clinician. One fascinating aspect of RBD is that the observer has, for the first time, the feeling of seeing "solid" mental images. Plus, RBD allows the study of whether eye movements follow dreaming imagery, whether non-dreamers do not dream or do not recall dreams, and whether motor or verbal learning is overtly replayed within dreams. Eventually, the directory of all behaviors, speech,

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and facial expressions during RBD will constitute a fascinating ethology of the dreaming process.

The first part of this chapter is devoted to the dream content during RBD, how much it is recalled, how it may differ from "normal" dreaming (in idiopathic RBD as well as in Parkinson's disease-associated RBD), and how RBD behaviors may correlate to dream recall (including the current debate about whether dreams evoke behaviors or behaviors evoke dreams and whether the content is systematically active/violent or not). The second part is devoted to how to use RBD as a (small) window to overtly approach the physiology of dreaming and cognitive processes during REM sleep. It includes how RBD can be used to demonstrate if non-dreamers do actually dream and if eye movements are tightly coordinated with the general behavior including dream images during REM sleep, to test the replay hypothesis for sleep-related verbal and motor memory consolidation and to study the phonetics and semantics of language during sleep.

17.2 Characteristics of Dream Content During RBD

The observed vocalizations or behaviors during RBD often correlate with simultaneously occurring dream mentation, leading to the frequent report of "acting out one's dreams." The behaviors usually manifest as attempted enactments of unpleasant, action-filled, and violent dreams or nightmares in which the individual is being confronted, attacked, or chased by unfamiliar people or animals. Typically, at the end of an episode, the individual awakens quickly, becomes rapidly alert, and reports a dream with a coherent story. The dream action corresponds closely to the observed sleep behaviors. We will examine the evidence supporting the presence of dreams upon awakening from an RBD episode, the evidence supporting the concordance between the action in dreams and in reality, and the evidence for/against predominance of violence in RBD dreams.

17.2.1 Dream Recall upon Awakening from REM Sleep Behavior Disorder

The recall of a dream upon awakening from REM sleep in normal subjects is frequent but not systematic, as 20–23% of REM sleep awakening do not elicit any dream recall [4–6]. Similarly, if most patients report a dream upon awakening from an RBD episode, this is not a universal finding. Sixty-four patients with RBD and Parkinson's disease were interviewed with a systematic questionnaire in Italy [7]. Spontaneous awakenings from the RBD were reported as often or always in 40.3%, sometimes in 22.6%, and never in 35.5% patients. Among them, 66.1% were always/often readily awoken, whereas it was only sometimes the case in 19.4% and never the case in 3.2%. The orientation upon awakening was frequently good in most (88.7%) patients, but occasional in 4.8% and absent in 1.6%. Dream content recall upon awakening was often present in 59.7% of

patients, sometimes in 33.9%, and never in 1.6%. In 122 patients with idiopathic RBD in Barcelona, 93% recalled some unpleasant dreams, but 7% had no recall of abnormal dreams [8].

17.2.2 Dream-Behavior Isomorphism

Because patients who are awakened immediately after a behavioral episode during RBD frequently report a dream content that is congruent with the objective behavior observed prior to awakening, these behaviors are believed to represent the acting out of dreams while sound asleep and unaware of one's surrounding. The concordance between the dream actions (reported upon awakening from these behaviors) and the behaviors observed by the bed sharer or by clinicians on the video-monitoring during proven REM sleep in the sleep lab is called isomorphism. The existence of a dream-action isomorphism has been supported in numerous case reports by history and by direct observation in the sleep laboratory (Table 17.1). It has been tested in a single controlled study and debated in the context of the analysis of REM sleep-associated twitches in developing rats.

Table 17.1 Dreaming characteristics in patients with RBD

Characteristics/population	Results	References
Dream recall upon awakening from a motor RBD event		
Interview of 64 PD patients with RBD	66% readily awoken; dream recall often present in 59.7%	[7]
Unpleasant dreams upon awakening from a motor RBD event		
Interview of 64 PD patients with RBD	91% of RBD dreams include fighting in response to danger	[7]
Dreams they remember in the last month, in 41 patients with RBD vs. 35 controls	More aggression and animals in patients' than controls' dreams	[21]
Interview of 122 patients with idiopathic RBD	93% recall unpleasant dreams, 7% recall normal dreams	[8]
Possibility of pleasant dreaming activity during enacted dreams		
Interview and sleep monitoring in a clinical sample	18% of patients with Parkinson's disease enacted both pleasant and unpleasant dreams; numerous examples of nonviolent dreams and behaviors in patients with RBD	[12]
Dreaming/motor activity isomorphism		
Incidental reports by spouses	Clear dream/action concordance	[9–14]
Incidental observations on video-polysomnography	Scenic RBD behaviors followed by congruent dream recall	[12]
Blind matching of four possible/different dream reports with one videotaped RBD motor behavior in (each of) six patients with RBD	The matching was 33%, above the 25% random matching rate	[15]

17.2.2.1 Home Reports

There have been many incidental reports of clear dream-action isomorphism in RBD [9–14]. As clinicians, we are fond of such stories, because they are important for the diagnosis of the disorder, and unravel all the beauty of the dreaming life, even when dreamt events are rather nightmarish. In our series of 53 patients with Parkinson's disease and RBD, patients and spouses revealed several examples of perfect dream-action isomorphisms [11]. A patient dreamt that he was a police duck, flying after a pigeon thief; in real life, his wife observed him squatting on the bed, waving his arms as if flying, and shouting "pin pon" (the two-tone sound of a siren) with a duck's voice. Another man dreamt that he was in a canoe, attacked by caimans, trying to make them flee. In reality, he was sitting on the bed rowing without paddles, shouting "Help, caimans!", getting hold of a heavy oak bedside table, and throwing it across the room. Another patient dreamt he was a knight fighting with a sword to save his endangered ladylove; in reality, he was lying in his bed, fighting with an invisible sword, with great agility and shouting "Manon, Charlemagne!" (a medieval battle cry). In 222 patients with idiopathic RBD in Barcelona, some examples of isomorphism are given [14]. A male, aged 65, roared loudly and woke up, recalling a dream where lions were attacking him. A 63-year-old man dreamt that someone was chasing him to the point that he jumped in a river to escape; instead, he jumped out of his bed. A 64-year-old woman dreamt that someone puts a straitjacket on her; in real life, she struggled to take off her pajamas while kicking. A 63-year-old man dreamt that a dog was attacking him; asleep in his bed, he said: "a dog wants to eat me" (note the excellent isomorphism here, provided by the concordant sleep talking). In *Paradox Lost* Carlos Schenck reported on a man who hit his head against the wall, later recalling he was fighting against a mean dog [10].

17.2.2.2 Reports of Behaviors Concordant with Dream Recall During Video-Polysomnography

Apart from the history, an excellent matching between behaviors and further dream recall was observed in several cases [12]: a retired carpenter with narcolepsy was studied in the sleep lab and reported after awakening of having drawn and then built a stair with a plank in a dream. During the corresponding REM sleep episode, he shook an invisible hand, while he introduced himself as "I am Mr. Do." Later, he seemed to draw while whistling, to measure, pull, to his tools and then hit something with a fictive hammer for almost 10 min. A patient with idiopathic RBD dreamt of meeting a minister. The minister told him: "What? You do not salute an old friend like me." So he shaked his hand. In the corresponding REM sleep episode, you can see him sitting in bed and shaking an invisible hand while saying "Good day!" Only the end and active part of the dream scenario was enacted out in this case. A patient with Parkinson's disease reported a long dream in which he was a knight in the medieval time, riding his horse around France for a whole day. Then he rested in a small inn, sleeping on the hay on the floor, as a Saracen fighter entered the room through the window and threatened to kill him with a scimitar. The knight could not grab his sword but found in the hay a wheat flail and defended himself

Fig. 17.1 Representation of the isomorphism between an RBD behavior and the concomitant dream (Artist: Cléa Arnulf, based on the video clip and report of the patient). This patient recalled a long medieval dream during which he was defending himself with a wheat flail against a Saracen fighter attacking him with a scimitar. Instead, in the actual bedroom, he was handling the tubing of his positive airway pressure device to defend himself

with it. In the corresponding video-polysomnography, the patient, lying on his back and sometimes sitting in bed, fought firmly back at an invisible aggressor, and placed on his right hand, using his fist on the positive airway pressure tubing (Fig. 17.1). All these cases of scenic behaviors illustrate an excellent dream-behavior correspondence, at least for some parts of the dream scenario. However, one may notice that despite the recalled dreams being often long, the observed behaviors were short, possibly acting out only a (final?) part of the dreamer's dream mentation.

17.2.2.3 Formal Testing of the Dream-Behavior Correspondence

The congruence between the actual action performed by RBD patients during REM sleep and the dream content later recalled has been formally assessed in a single study [15]. Seven blind judges had to match a set of four possible dream contents (collected upon serial awakenings after 10 min of REM sleep in the second and successive episodes, in patients with Parkinson's disease, with and without RBD), of which just one of the dream contents was correct, with motor behaviors videotaped during REM sleep in six patients with RBD. The possibility to match adequately one of these dreams by chance was 25%, as there were four choices. Of the 35 REM sleep awakenings performed, a total of 17 (48.6%)

motor-behavioral episodes with recalled dream content were obtained. The average of correctly identified video-dream pairs was 39.5% (range 0–100%), which is significantly above the chance level, but still in less than half of episodes. One may wonder why the concordance did not approach 100%. However, one should note that this video series contained mainly simple movements, which are difficult to match with any behavior, whereas scenic behaviors were rare, despite being easier to match, due to the complexity of the behaviors and vocalization observed in these cases [15]. An example of dream-behavior pair is, for the motor part on the video, "raising both arms for several seconds, then grabbing for something. Few lip movements resembling talking without sound. Intermittent small distal limb and head movements. No apparent emotion." And the corresponding dream report was **"**I was in a competition. There was a race and we had to run, and step into open tubes. Open tubes floating in a lake. We had to get there. We had to run to the tubes, then jump into them and then paddle to the other side of the lake. Then, on the other side, we had bicycles, and we had to ride to our homes. But there was a bridge to cross, it was bottle-like, very narrow. There was a little fight over who was the first. I tried to get to the bridge first. There was a fight for the best position. I was part of this fight. Actually, it was a lot of fun. I was pleased." This is a complex experiment in a small sample, requiring patients with RBD to accept being awakened three times per night and report immediate dream recall. So far, it has not been reproduced.

17.2.2.4 Dreams Evoking Behaviors or Behaviors Evoking Dreams?

The RBD-associated behaviors are often thought to result from a dysfunction involving atonia-producing neural circuitry in the brainstem, thereby unmasking cortically generated dreams, exactly as if a curtain was placed in front of a theatrical play (normal, atonic condition) or instead raised up (RBD condition). This view may however be too simplistic. It is challenged by two conditions: REM sleep with enhanced chin (postural) muscle tone but without RBD (remembering a raised curtain without any theatrical play behind it) in some patients and by phasic movements despite preserved chin atonia (a theatrical play made visible through the atonia curtain), presumably indicating that over-activation of the phasic motor system has overwhelmed REM atonia. If the loss of atonia is an admitted fact, the "dreaming" and cortical origin of behaviors in RBD is still a debate among scientists. On the one hand, numerous complex behaviors (including speech and learned behaviors, e.g., smoking, dealing cards, lecturing) can be observed during RBD [16]. These are not archaic behaviors and could not result from a source other than the motor cortex.

On the other hand, the group of Blumberg (Iowa, USA) has suggested another source apart from the motor cortex for the RBD behaviors, based on studying the central drive of muscle twitches during REM sleep in newborn rats [17]. Early studies in animals showed that REM sleep twitches were not driven by the motor cortex, because they persisted even when the brain areas located above the peduncle were removed or disconnected from the brainstem, indicating that the generator of twitches was located between the medulla oblongata and the superior colliculus

[18]. Later, Blumberg et al. showed that the cortical motor activity increased during REM sleep, but it did so immediately after (and not immediately before) twitches. Because the latencies from twitches to peak neural activation were greater than 100 ms, their conclusion was that the sensory feedback (i.e., re-afference) from twitching limbs was driving activity in motor cortex [19]. Notably, during wakeful movements, the nervous system drives movements and simultaneously generates a copy of the motor command (the corollary discharge) to inform the sensory cortex of the expected changes. This process helps to distinguish sensations that are self-generated from those that are external. By contrast, during REM sleep the twitches are not accompanied by corollary discharges, and "surprise" the sensory cortex, and also trigger strong activity in the primary motor cortex that is not seen in response to passive movements of the tail when awake [19]. These twitches might contribute to an activity-dependent development of the spinal cord, cerebellum, and forebrain and to the construction of internal models.

Moreover, several authors mentioned that, in animals, the motor cortex is not even necessary to produce complex behavior; for example, chemical and electrical stimulation of some brainstem structures can produce defensive and aggressive behaviors in rats and monkeys that may resemble those reported in human patients with RBD. Accordingly, Mark Blumberg suggested that the brainstem (and possibly the red nucleus) could be one of the sources of the pathological movements and that sensory feedback from moving limbs could secondarily influence the content of dream mentation [17]. This reverse hypothesis, which is not incompatible with the previous, "descending" hypothesis (behaviors are the products of dreaming), suggests that a brainstem motor pattern generator of either simple movements (myoclonic twitches) or patterned behaviors (e.g., defense, attack) would first evoke movements, which in turn, via sensory feedback, would evoke dreams incorporating these stimuli.

17.2.3 Violent Dreams

17.2.3.1 A Predominance of Fighting Behaviors

Most descriptions emphasize the forceful and violent aspect of the RBD-associated motor behaviors (Table 17.1), which are usually associated with vivid, unpleasant, and active dreams [20]. The dreams associated with RBD are usually different from those experienced by patients before RBD onset, although this assertion is difficult to prove, as none completed a dream diary prior to RBD onset. The patients report enacted dreams containing more elements of aggression and animals than control subjects when they are asked about the dreams they remember in the last month [21]. In 58 patients with Parkinson's disease plus RBD, the most commonly associated dream is fighting in response to danger (91%), whereas pleasant activity is reported in 20% of patients and daily activity in 22% of patients [7]. In 188 patients with idiopathic RBD recalling unpleasant dreams [14], the following contents were reported: attacked by someone (76.8%), arguing with someone (63.5%), chased by someone (55.7%), falling from a cliff (47.8%), and attacked by an animal (39.9%, involving, in descending order of frequency, dogs, snakes, lions, bulls, horses,

insects, cats, rats, tigers, pigs, wolves, crocodiles, cows, moles, piranhas, wild boars). Dreams containing children in danger were reported by 12.8% of patients. In a group of 66 patients with Parkinson's disease and RBD, all reported they had at least once some violent behaviors [12].

17.2.3.2 Threat Simulation Theory: Fight vs. Flight?

A mechanism of this violence during RBD could be related to a general function of dreams, as suggested by the threat simulation theory [22]. This theory suggests that the function of dreaming is to simulate threatening events in a virtual environment and to rehearse threat perception and threat avoidance for the evolutionary purpose of increased survival. These dreams of fighting wild animals and aggressors are not a consequence of personality changes, as they contrast with the placid personality and absence of aggressiveness during the daytime in RBD patients [13, 21]. Whether the threat simulation theory applies to RBD dreams (vs. sleepwalking/sleep terrors) was studied in a group of 24 subjects with RBD vs. 32 subjects with sleepwalking or sleep terrors [13]. Subjects completed aggression, depression, and anxiety questionnaires. The mentations associated with sleepwalking and RBD behaviors were collected over their lifetime (as far back in time as they could remember) and on the morning after video-polysomnography. The reports were analyzed for complexity, length, content, setting, bizarreness, and threat [23, 24]. Almost all of the sleepwalkers and patients with RBD reported enacted dreams. The enacted dreams of subjects with RBD were more complex and less bizarre than the dreams of sleepwalkers (who had more discontinuous mentations), but the dreams were similar in length in both groups when dreams were reported over their lifetime. Aggression was more frequently observed during the RBD-enacted dreams than during sleepwalking. Up to 70% of sleepwalking dreams and 60% of RBD dreams involved a threat. There were more misfortunes and disasters in the sleepwalkers' dreams, and there was more aggression in the RBD dreams.

The response to these difficulties differed between the groups, as the sleepwalkers mostly fled from a disaster, while most (75%) patients with RBD counterattacked when assaulted. These major differences in the type of threat and in the dreamer's response were reminiscent of the fight-or-flight response to threats. Subjects with RBD defended themselves, and less frequently their family from attackers (mostly human strangers), and rarely were the first attacker in the dreamt fight (6%). The RBD-enacted dreams involved more aggression when retrospectively collected over a lifetime span than when prospectively collected on the morning following the sleep monitoring, suggesting a recall bias (dream recall likely is enhanced when the dream-enacted behaviors lead to an awakening or injuries, which more frequently occurs when the dream content is violent). In the dreams of normal healthy subjects, aggressive behaviors are twice as frequent (65%) during REM sleep compared to NREM sleep. Therefore, RBD-associated aggression may be a disorder of enacting dreams (aggression dreams because aggression is frequent in REM sleep dreams) rather than a disorder of dreaming. Alternatively, these threats in RBD may be the exacerbation of systems that train humans to appropriately react during the daytime to a wide spectrum of dangers.

17.2.4 Nonviolent Dreams

Some dream-enacted behaviors can be prolonged and scenic. They include gesturing, reaching, grabbing, arm flailing, slapping, punching, kicking, sitting up, and leaping from bed. Nonviolent elaborate behaviors, however, occur in 18% of patients with Parkinson's disease and RBD (coexisting in this case with violent behaviors within the same or other nights), as well as in patients with idiopathic RBD and RBD associated with other diseases [12]. They include eating and smoking (fictive behaviors in the absence of real food or cigarettes); picking apples; dancing; teaching; gesturing thumbs-up; kissing; giving a lecture; selling textiles; clapping at a show; sorting buttons; displaying pelvic, coitus-like thrusting; masturbating; urinating (while dreaming of urinating in a river as a child); scoring a goal; bicycling; greeting; flying; building a staircase; getting dressed and inspecting the army; and searching for treasure. Most behaviors are learned behaviors in accordance with the cultural and social context of the patient. Patients display various types of vocalizations, such as mumbling, talking, shouting, swearing profanities, laughing, and crying [20]. However, the majority of patients mumble or speak during RBD, sometimes quite easily, and they speak with appropriate prosody, gestures, fluency, and syntax [12]. Singing and whistling are possible with correct musicality, and the local dialect is maintained [12].

The Barcelona team looked at occasional nonviolent elaborated activities reported by the spouses of 203 patients with idiopathic RBD: action-filled sports were present in 15.8% of RBD dream content, including soccer (81.3%), then boxing (6.3%), and skiing, basketball, motorcycling, and cycling (3.1% each). Love (kissing in three cases), giving a political speech (three cases), teaching a lesson (one case), shuffling, picking things, and riding were also reported [14]. In one patient, a behavior resembling sexual intercourse with an imaginary partner and accompanied by a disgusting comment occurred on a single night, as reported by his wife. Patients who experienced these nonviolent behaviors also displayed aggressive behaviors during the same or different nights.

This possible enactment of nonviolent dreams is also observed in patients with Parkinson's disease, with or without RBD [25]. When dream reports are collected daily over several weeks in patients with treated RBD and controls, there are no differences in the content of the dreams, suggesting either a bias of recall shifted toward selectively remembering the enacted violent dreams or a benefit of clonazepam on the abnormal dreaming process itself [26]. Furthermore, when 69 dream reports are systematically collected upon provoked awakening from NREM and REM sleep in patients with Parkinson's disease with (n = 9, mostly during RBD movements and sometimes during quiet REM sleep) and without (n = 6) RBD and analyzed for content, action-filledness (actions, environmental events), vividness (cognition, emotions), intensity, and threatening elements (including aggression) are not different between groups, although emotions are more negatively toned in those with than without RBD [27]. Further, patients with RBD tend to act out their most intense dreams, and negative dreams may more likely be acted out than positive dreams [15]. Consequently, the acted out dreams are the ones most likely to be

remembered afterward. The retrospective memory bias for intense and aggressive dreams may thus reflect these infrequent tip-of-the-iceberg dreams (and not be a bias after all), although the majority of dreams of patients with RBD are not altered in any way. This interesting study supports the idea that the dream content is similar in patients who enact or not their dreams, presumably suggesting that there is no change in dream content in Parkinson's disease with RBD but a change in muscle atonia network.

17.2.5 A Change in Dreaming Caused by Parkinson's Disease?

Compared to normal controls, the dreaming activity changes in Parkinson's disease. As many as 46% of patients report altered dream phenomena, including a high frequency of nightmares and violent or unpleasant dreams, especially when levodopa therapy is introduced [28–31]. Cipolli et al. examined the narrative quality of dream experience in 13 patients with Parkinson's disease after provoked awakenings from REM sleep. Patients had a dream recall frequency (71.9%) in REM sleep within normative ranges. Plus, the length of a dream as a story paralleled their cognitive level (score in the Mini-Mental State Evaluation), but not their age, disease course, or dose of levodopa. The organization of dream contents into coherent episodes paralleled their language comprehension (Token test) [32]. In early Parkinson's disease stages, patients' dreams differ from those of the control group in features related to aggressive actions (in which they frequently had a passive role), the presence of animals, a relatively higher frequency of friendly acts toward other characters, and a lower frequency of bodily misfortunes [33]. As the altered dreaming correlated with frontal cognitive impairment and not with the presence or absence of concomitant RBD, the authors speculate that the higher level of aggression reflects intensification of the limbic preponderance during sleep due to a loss of the prefrontal regulatory influence. In contrast, Borek et al. found a relatively higher frequency of aggressive features in patients with Parkinson's disease, with vs. without RBD (with no further difference in men vs. women with RBD), although dreams were less aggressive in women than in men [25].

The altered dreaming activity was associated with more frequent awakenings and illusions/hallucinations, but not with specific (levodopa, dopamine agonist) medications [30]. A "kindling" phenomenon, starting from altered dreaming and evolving toward illusions, hallucinations of minor then major severity, and eventually psychosis, was suspected at that time [28]. However, the presence of vivid dreams/nightmares correlated with concurrent hallucinations, but did not predict the future development of hallucinations when they occurred in non-hallucinators in a 10-year prospective study [34]. This interest toward vivid dreams and nightmares as a first step toward hallucinations and psychosis did not include the concept of RBD, which was not yet identified as a disorder at this time [28]. When RBD was later examined at entry in the cohorts, it proved to be a major determinant for concurrent and incident hallucinations, as well as the later development of psychosis and

dementia [34, 35]. More recently, the presence of RBD in 80 dementia-free patients with PD for a mean 5.7 years was the highest (odds ratio, 49.7) risk factor for developing dementia within the 4 next years, much higher than classical risk factors such as cognitive impairment or age [36]. Illusions and hallucinations were also predictors of dementia, with odds ratios of 8 and 10 [36]. It was not specified, however, whether RBD was a predictor of hallucinations and psychosis in this group of patients.

17.2.6 Are RBD Dreams Occurring During Genuine REM Sleep?

Because visually elaborate dreams are closely associated with normal REM sleep, the report of complex dreams, congruent with the observed sleep behavior, in patients awakened from an RBD episode constitutes convincing evidence that RBD is a manifestation of normal REM sleep (apart from the motor dyscontrol). Furthermore, most patients with RBD have no reflexive consciousness when they exhibit movements during the RBD episodes, as illustrated by a 74-year-old patient with narcolepsy, monitored while his wife was present in the room [37]. During an RBD episode, he whistled and seemed to draw and take measures (he dreamt that he was building a stair). His wife, thinking that he was awake and eager to be unhooked from the electrodes, told him not to move and to wait for the nurse. The patient needed several seconds before reacting; then he woke up and answered "What?" [she repeated her remark] "I did not say anything, I was sleeping." His wife concluded: "Oh, just I thought… So you were dreaming!" Thus, the patient was able to qualify his previous state as sleep and his present state as awake, strongly suggesting that RBD is a within-sleep-state phenomenon. In the same study, a patient was snoring during RBD behaviors, another had a penile erection (associated with a fighting behavior), and another one had loss of reflexive consciousness during the motor episodes. Taken together, these respiratory, cognitive, and autonomic clues support the concept that RBD occurs within genuine REM sleep and does not emerge from it. If this assumption is right, RBD (and its overt motor, autonomic, and cognitive features) could be used as an original model to study some mechanisms of normal REM sleep. For example, the penile erection associated here with overt fighting in RBD provides additional evidence that REM sleep-associated penile erection is an autonomic automatism unrelated to sexual dreams.

17.3 RBD as a Model to Shed Light on the Dreaming and Cognition Processes During Sleep

The congruence between dream enactment and concomitant dream content during RBD behaviors is a potent tool to test various hypotheses about dreaming and cognitive (e.g., memory, language) processes using the objective measures of REM sleep-associated behaviors, mimics, and vocalizations (Table 17.2).

Table 17.2 Contribution of RBD studies to the study of cognition and dreaming processes during REM sleep

Domain	Findings	References
Dream recall from REM sleep in non-dreamers	Non-dreamers exhibiting complex RBD were described, supporting the hypothesis that non-dreamers do dream, but do not recall dreams	[45]
Eye movements in association with dreaming images	Patients with goal-directed behaviors during RBD had eye movements directed to the target of their behavior and dream images, suggesting eye movements, behaviors, and dream images are co-organized by the sleeping brain	[47]
Procedural memory and consolidation during sleep	A recently learned motor sequence was partially replayed during a sleepwalking episode but not during RBD episodes	[55]
Verbal memory and consolidation during sleep	A recently learned verbal story was partly replayed with maintained meaning during REM sleep	[56]
Language	Language during REM sleep is grammatically correct. Verbal abuse outnumbers polite language	[58]

17.3.1 RBD as a Model to Support That Non-dreamers Do Dream

17.3.1.1 The Enigma of Non-dreamers

Dreaming is defined as mental activity during sleep [38]. It has long been solely accessible by the recollection of the dreamer after awakening. However, the frequency of dream recall varies considerably among individuals and within one individual from night to night, as well as with the method used to measure dream recall. Adults report, on average, 1–2.8 dream recalls per week in a dream questionnaire [39, 40] and 2.38 dream recalls per week when a home dream diary is completed [41], whereas there are substantially higher recall rates (77–90%) following REM sleep awakenings and also following NREM sleep awakenings (50–74%) in a sleep laboratory [4, 42].

Non-dreamers occupy an extreme end in this spectrum of individual differences in dream recall frequency. The incidence of adults who report on a questionnaire that they never dream varies from 2.7 to 6.5% [43, 44]. However, when questioned by phone, most of the same individuals report that they had an experience of dreaming (previously as an adult or child), which leads to an estimate of 0.38% of a clinical sample of adults who have never ever experienced any type of dreaming [44]. When awakened at the end of REM sleep periods in a sleep laboratory, the same non-dreamers did not report any dreams, even when a broad definition of dreaming was used that included thoughts, feelings, and emotions [44]. This group of individuals does not differ, based on polysomnography, clinical or demographic variables, from a comparable group of low dreamers that occasionally reports dreams when awakened in a sleep laboratory. This finding demonstrates that dreaming may not be a universal experience. Whether these non-dreamers either have no dream production or do have recall that could not be tested because there is no reliable marker of dreaming activity to be contrasted with dream recall remains an open question. These fascinating experiments regarding dream recall postulate that

dreams are not directly accessible. Consequently, the study of dreaming has been restricted to the analysis of recalled sleep mentation after spontaneous or provoked awakenings. However, this limitation may be circumvented by the discovery of RBD. Because patients awakened immediately after a behavior during RBD frequently report a dream content that is congruent with the objective behavior observed prior to awakening, these behaviors are believed to represent the acting out of dreams while sound asleep and unaware of one's surrounding.

17.3.1.2 Non-dreamers with RBD Exist and Do Enact Dreams

To determine whether non-dreamers do not produce dreams or do not recall them, we identified subjects with no dream recall and with dreamlike behaviors during RBD [45]. All consecutive patients with idiopathic RBD or RBD associated with Parkinson's disease who underwent a video-polysomnography were interviewed regarding the presence or absence of dream recall, retrospectively or upon spontaneous arousals. The patients with no dream recall for at least 10 years and never-ever dreamers were compared with dreamers with RBD regarding their clinical, cognitive, and sleep features. Of the 289 patients with RBD, eight (2.8%) patients had no dream recall, including four patients who had never-ever recalled dreams and four patients who had no dream recall for 10–56 years. All these non-dreamers exhibited, daily or almost nightly, several complex, scenic, and dreamlike behaviors and speech, which were also observed during REM sleep on video-polysomnography (e.g., arguing, fighting, and speaking). They did not recall a dream following sudden awakenings from REM sleep. These 8 non-dreamers with complex behaviors during RBD did not differ in terms of cognitive, clinical, treatment or sleep measures from 17 dreamers with RBD matched for age, sex, and disease.

The scenic dreamlike behaviors reported and observed during REM sleep in the rare non-dreamers with RBD (even in the never-ever dreamers) provide strong evidence that non-dreamers produce dreams, but do not recall them. Therefore, RBD provides a new model to evaluate cognitive processing during dreaming (and its enactment) and subsequent recall. Here is the paradox of RBD: dreams are thought to represent personal experiences; however, in the case of scenic behaviors and complex speeches, an external observer can sometimes know or guess part of the sleep mentation of the dreamers instead of the dreamers themselves (at least when they have forgotten everything following awakening). Naturally, the observer cannot see the images or hear the sounds experienced by the dreamer; however, he has privileged visual and auditory access to at least part of the scene played (and mimicked) by the dreamers.

Thus, RBD-associated behaviors may be considered materialized mental images of which some parts (the motor, facial expression and verbal parts) are made visible to the external observer, while they may not be encoded or recalled by the dreamer. RBD is a unique condition because there are no other conditions in which one may know instead of others what they are thinking and experiencing. This condition may question the very definition of dreams: if dreams are mental contents that occur during sleep and are recalled following awakening, then can RBD behaviors without dream recall be classified as dream-enacting behavior (or apparently dream-enacting behavior)? At this point, it would be fascinating to compare the functional brain

imaging of a patient with RBD during behaviors associated and not associated with dream recall following subsequent awakening. This study would help to determine the brain substrates of encoding during dreaming and subsequent recall.

17.3.2 RBD as a Model to Determine Whether the Eye Movements Scan Dream Images During REM Sleep

Rapid eye movements (REMs) and complex visual dreams are salient features of human REM sleep. However, it remains to be elucidated whether the eyes scan dream images, despite studies that have retrospectively compared the direction of REMs to the dream recall recorded after having awakened the sleeper. Determining the correspondence between eye movements and dream imagery is challenging due to the use of varying and flawed methodologies, as well as amnesia and a lack of clarity in dream recall. Furthermore, in the awake state, the eyes and head work in concert to produce gaze [46]. Only with the summation of head and eye activity does an isomorphism between gaze and target become apparent. In normal REM sleep, atonia spares the extraocular muscles but not the neck muscles so that the head cannot move, rendering the parallel between observed eye movements and the subject's description of gaze (in the dream) uncertain.

One way to circumscribe these methodological problems (recall bias, retrograde assessment, neck-eye movement combination) in humans was to study subjects with RBD (in whom the neck is not paralyzed), to determine directly whether the eyes move in the same directions as the head and limbs [47]. In 56 patients with RBD and 17 healthy matched controls, we monitored eye movements by electro-oculography in four directions (right, left, up, and down) and synchronized with video and sleep monitoring. The RBD-associated behaviors occurred two times more frequently during REM sleep with REMs than without REMs, and more often during or after REMs than before REMs, a result previously observed by the Innsbruck (Austria) and Pavia (Italy) teams [48, 49]. The density, index, and complexity of REMs were similar in patients with RBD and controls. When REMs accompanied goal-oriented motor behavior during RBD (e.g., grabbing a fictive object, hand greetings, climbing a ladder, sending a kiss with the hand), which happened in 19 sequences, 82% were directed toward the action of the patient (same plane and direction). When restricted to the determinant REMs, the concordance increased to 90%. Rapid eye movements were absent in 38–42% of behaviors. This directional coherence among limb, head, and eye movements during RBD suggests that, when present, REMs imitate the scanning of the dream scene. Since the REMs are similar in subjects with and without RBD, this concordance can be extended to normal REM sleep. However, these results do not mean that the dreamer actually watches the dream images in RBD. Rather, one common system may simultaneously activate dream images as well as eye and body movements in a coherent fashion [50]. This scenario would support the results from several experiments, including the presence of REMs in the absence of any kind of vision (in neonates,

congenitally blind humans, cats without visual cortex, pontine cats), as well as the temporal association between ponto-geniculo-occipital spikes and REMs in cats.

17.3.3 RBD as a Model to Test the Replay Hypothesis for Sleep-Related Memory Consolidation

17.3.3.1 Sleep and Memory Consolidation

It is well established that sleep facilitates plastic changes that underlie the consolidation of recently acquired knowledge. The prevailing hypothesis states that the neural traces coding for the newly acquired information are reactivated during sleep, thus fostering memory consolidation. In rats and birds, specific patterns of neural activity associated with recent waking behavior are spontaneously replayed during subsequent sleep [51, 52]. Similarly, functional neuroimaging studies in humans have shown that brain regions involved in motor skill learning are reactivated during post-training sleep [53]. Dreams also contain a high proportion of recent waking experiences [54]. However, direct evidence for a replay of temporally structured information during human sleep is still lacking. We used the RBD and the NREM parasomnia models as a way to directly observe mental content during sleep and whether it incorporated recent memories. At the time of these studies, it was suggested that procedural memory was trained during REM sleep, whereas verbal memory was trained during NREM sleep. Amazingly (you never find what you expect), the contrary was observed in our experiments: a kind of verbal replay was observed during RBD, whereas a partial motor replay was observed during NREM parasomnias, as described below.

17.3.3.2 Is There Any Reenactment of a Recently Learned Motor Task During RBD?

In a motor study, 20 patients with RBD and 19 sleepwalkers were trained on a modified version of a serial reaction time task, which is known to robustly benefit from sleep [55]. We examined whether, during video sleep recordings, the patients would replay fragments of a recently trained sequence involving large arm movements. Both patient groups showed learning of the intensively trained motor sequence after sleep. However, a sleepwalker reenacted a fragment of the recently trained motor behavior during one sleepwalking episode: she raised both arms in the premotor posture and then gently pressed on a fictive button, as during the awakened motor task. The patients with RBD exhibited several complex behaviors during REM sleep on the two experimental nights (i.e., hand movements, defense posture, kicking, punching, reaching, smiling, pointing, leaping out of bed, whispering, and speaking). No obvious motor replay of the task was identified among these REM sleep-associated behaviors. Actually, the probability of observing overt behaviors in patients with RBD and in sleepwalkers is low, making this finding of overt replay highly remarkable. Indeed, patients with RBD exhibit complex, purposeful behaviors during only 0.1–20% of the total time spent in REM sleep [55].

17.3.3.3 Is There Any Reenactment of Verbal Episodic Memory During RBD?

In this study, we aimed to determine if sleep talkers with RBD would utter during REM sleep sentences learned before sleep and to evaluate their verbal memory consolidation during sleep [56]. Eighteen patients with RBD and ten controls performed verbal memory tasks (the Free and Cued Selective Reminding Test and a 220–263 word long modified Story Recall Test) in the evening, followed by nocturnal video-polysomnography and morning recall (nighttime consolidation). They also learned a second list of words and a second story, in the morning, followed by a recall in the evening after 11 h of wakefulness (daytime consolidation). Sleep-related verbal memory consolidation was maintained in patients with RBD (+24 ± 36% words, compared a worsening during daytime consolidation) as in controls (+9 ± 18%, $p = 0.3$). Eleven patients with RBD spoke during REM sleep and pronounced a median of 20 words, which represented 0.0003% of sleep with spoken language. A single patient uttered a sentence judged to be semantically (but not literally) related to the text learned before sleep. The text to be learned was a long newspaper text about an unemployed single mother wandering about Chicago streets in 1911. She was carrying her newborn just after having giving birth, was looking for job, was unable to find one, and eventually strangled her infant. Cradling the dead child in her arms, she then carried its body several miles away and threw him in a bin. One of the patients with RBD uttered the following words during REM sleep: "Don't put me on like this…where did you wait for me? You must explain this, eh? I want an explanation now, you're a little slut because you go hanging about in the streets… and you come…I know you very well, you know?... I know you." The patient had no dream recall the next morning. This case demonstrated that the learned material was incorporated, at least, at the semantic level (a pitiful woman "slut," wandering in the street, as had the young mother of the story) during sleep talking, unbeknownst to the sleeper himself. This overt evidence provided some new insight into the creative activity of the sleeping brain.

17.3.4 Language During RBD as a Way to Access Language Processing During Sleep and Dreams

Sleep talking (also called somniloquy) is a fascinating and enigmatic phenomenon. The verbal utterances while asleep can be quite loud, ranging from simple mumbling sounds to loud shouts. Several authors noticed that most sleep speech is rare (a frequent sleep talker has to be monitored for at least four nights to obtain some verbal material) and brief and consists of a few words rather than extended remarks [57]. However, the syntax, semantics, and content of sleep speech have not been studied yet, despite the fact that human speech is a complex, high-level function in awake people.

Patients with RBD sleep talk during REM sleep, but the semantic and linguistic properties of RBD-associated language have been only recently studied [58]. In 129 patients with RBD, 75% of 548 REM sleep utterances were nonverbal, containing

mostly mumbles (40%), whispers (25%), laughs (20%), shouts (17%), lip movements without sound like a silent speech (12%), and moans (9%). Humming (2.1%) and crying (0.3%) were rare. The 211 verbal speech episodes contained a mean 8 words. The sentences were mostly affirmative (75%), but 20% were negative and 21% were interrogative. Offensive language was surprisingly frequent and outnumbered polite language. One may imagine that it parallels the dramatic and confrontational mental concerns of the dreamers (one would use verbal violence, including profanity, more readily when fighting an aggressor or when being in danger) during RBD or that it reflects some degree of social disinhibition during sleep. In this regard, a relative hypoactivity of the inferior and middle frontal cortex (which contains networks developed by education) has been demonstrated during REM sleep compared to wakefulness in functional brain imaging, possibly underlying the loss of politeness in many nocturnal speech episodes. There was a higher rate of profanities in men than in women during sleep talking, which may reflect gender differences in waking life or more physical threats in male RBD-associated dreams. Notably, nasty words were more frequent in NREM parasomnias than in REM sleep with RBD, with one third of speech episodes in NREM sleep containing profanities, and the nature of verbal offense differed between sleep stages. Verbal abuse in REM sleep with RBD lasted longer and was mostly directed toward insulting or condemning someone (with factors of intensification including more marked prosody and volume as well as repetitions), whereas undirected swearing predominated in NREM sleep. Again, these stage-related differences may reflect different mental activities, with more (aggressive) interactions with people in REM sleep in RBD, hence the insults and condemnations.

Conclusions

RBD unmasks part of the dream content, which allows studying the dreaming process in an "online" manner. To a certain degree, what is found within the unmasked material may also apply to normal REM sleep dreaming. The use of RBD to understand the cognitive processes during REM sleep is tightly dependent on the possibility to observe scenic behaviors, which are rare phenomena, compared to the number of simple, jerky movements without any clear purpose (at least for the observer) seen in the sleep lab context. There is a need for building video banks of all RBD behaviors during REM sleep, in order to share them and make progress with this line of research. Scenic RBD is a narrow, but fascinating, window upon dreaming. We think that what it may reveal from the normal (and pathologic) dreaming process is just the beginning. Let's be creative on this point!

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Part III

Diagnosis and Treatment

Diagnosis of REM Sleep Behavior Disorder

18

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18.1 Introduction

The *International Classification of Sleep Disorders* (ICSD), *Third Edition* (ICSD-3) [1], diagnostic criteria for REM sleep behavior disorder (RBD) rely on vocal and behavioral manifestations and additionally require a background of increased tonic and/or phasic electromyographic (EMG) activity in the polysomnography (PSG), thus seeming unequivocal at first sight. However, when looking into the details or in particular situations, the diagnosis of RBD is not always straightforward [2, 3], and even in the official diagnostic criteria, ambiguities remain, which will be discussed below.

18.2 Historical Development of the Criteria for RBD

In a historical context, RBD was first recognized as a diagnosis in the 1990 "International classification of sleep disorders: Diagnostic and coding manual" criteria [4], after the first systematic description in 1986 [5]. The first diagnostic criteria for RBD [4], initially listed as number six among the "parasomnias usually associated with REM sleep", required as minimal criteria limb or body movement associated with sleep mentation plus at least one of the following: harmful or potentially harmful sleep behaviors; dreams appear to be acted out; and sleep behaviors disrupt sleep continuity. In the ICSD-I revised (2001) [6], there was no change in these minimal RBD diagnostic criteria.

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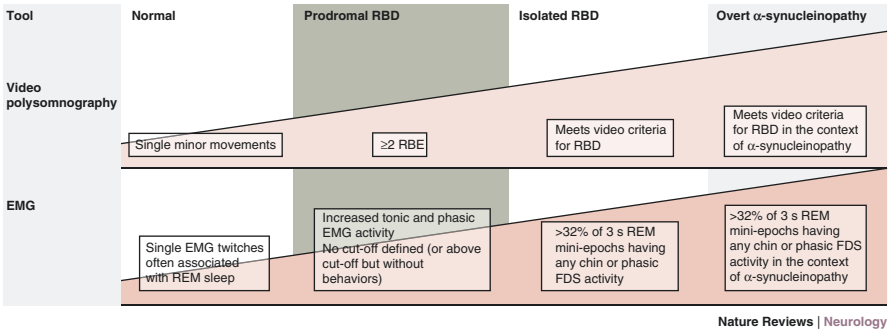

Fig. 18.1 Progression of neurophysiological and behavioral findings in RBD [8]. Neurophysiological and behavioral findings on polysomnography (PSG) and electromyography (EMG) progress along a continuum from normal to prodromal rapid eye movement (REM) sleep behavior disorder (RBD), isolated RBD (iRBD) and RBD with overt α-synucleinopathy. *FDS* flexor digitorum superficialis, *RBE* REM sleep behavioral events

In the 2005 ICSD-2 [7], the RBD criteria were slightly modified. At least one of the following was required: (1) sleep-related injurious, potentially injurious or disruptive behaviors by history and (2) abnormal REM sleep behaviors documented during PSG monitoring, as well as the absence of electroencephalographic (EEG) epileptiform activity and the exclusion of other disorders as possible explanation for the sleep disturbance. Therefore, the presence of RBD behaviors either by history or documented during video PSG (vPSG) was required, allowing a diagnosis of RBD even in the absence of a suggestive clinical history in case of clear RBD behaviors during the vPSG.

Over time the criteria changed from a focus mainly on the clinical history, which is important but has clear limitations, to a focus on vPSG, with documentation of movements/vocalizations and REM sleep without atonia (RWA). Moreover, over time it has been recognized that the well-known large or violent complex behavioral outbursts in RBD account for only a very small proportion of all REM-related movements [8]. Therefore, the requirements that behaviors are harmful/potentially harmful and the apparent "acting out" of dreams (which can be subject to interpretation variance in case of small movements) are not included anymore in the ICSD-3 [1]. Moving further in this direction, prodromal phases of RBD have been identified (see below, and Fig. 18.1) [8–10], which are not recognized by the current diagnostic criteria.

18.3 Diagnostic Criteria: Currently Valid and Accepted Standards to Diagnose RBD

The currently validated and accepted standards to diagnose RBD are shown in Tables 18.1, 18.2 and 18.3: the ICSD-3 [1] criteria (Table 18.1), the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and

Table 18.1 *International Classification of Sleep Disorders, Third Edition* (ICSD-3) [1]. REM Sleep Behavior Disorder Diagnostic Criteria

Criteria A–D must be met	
A.	Repeated episodes of sleep-related vocalization and/or complex motor behaviors[a,b]
B.	These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep
C.	Polysomnographic recording demonstrates REM sleep without atonia (RWA)[c]
D.	The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance use

[a]This criterion can be fulfilled by observation of repetitive episodes during a single night of video polysomnography
[b]The observed vocalizations or behaviors often correlate with simultaneously occurring dream mentation, leading to the frequent report of "acting out one's dreams"
[c]As defined by the guidelines for scoring PSG features of RBD in the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events

Table 18.2 The American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events [11]. Scoring Polysomnographic Features of REM Sleep Behavior Disorder (RBD)

1.	Score in accordance with the following definitions
Sustained muscle activity (tonic activity) in REM sleep: An epoch of REM sleep with at least 50% of the duration of the epoch having a chin EMG amplitude greater than the minimum amplitude demonstrated in NREM sleep	
Excessive transient muscle activity (phasic activity) in REM sleep: In a 30 s epoch of REM sleep divided into ten sequential 3 s mini-epochs, at least five (50%) of the mini-epochs contain bursts of transient muscle activity. In RBD, excessive transient muscle activity bursts are 0.1–5.0 s in duration and at least four times as high in amplitude as the background EMG activity	
2.	The polysomnographic characteristics of RBD are characterized by EITHER or BOTH of the following features:[N1,N2,N3]
	(a) Sustained muscle activity in REM sleep in the chin EMG (b) Excessive transient muscle activity during REM in the chin or limb EMG

EMG electromyography

Table 18.3 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [12]. Rapid Eye Movement Sleep Behavior Disorder Diagnostic Criteria (Only the Core Features are Reported)

A.	Repeated episodes of arousal during sleep associated with vocalization and/or complex motor behaviors
B.	These behaviors arise during rapid eye movement (REM) sleep and therefore usually occur more than 90 min after sleep onset, are more frequent during the later portions of the sleep period and uncommonly occur during daytime naps
C.	Upon awakening from these episodes, the individual is completely awake, alert and not confused or disoriented
D.	Either of the following: 1. REM sleep without atonia in polysomnographic recording 2. A history suggestive of REM sleep behavior disorder and an established synucleinopathy diagnosis (e.g. Parkinson's disease, multiple system atrophy)

Associated Events, Version 2.4 [11] (Table 18.2) and criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [12] (DSM-5, Table 18.3).

18.3.1 RBD Diagnostic Criteria in ICSD-3

The diagnostic criteria of the ICSD-3 [1] are reported in Table 18.1. A footnote on the criterion C, "polysomnography demonstrates RWA", links this criterion with the respective most recent version of the AASM Manual for the Scoring of Sleep and Associated Events [11] (Table 18.2).

The diagnostic criteria also mention that a provisional diagnosis of RBD can be made in patients with a typical history and typical video documentation in video PSG but who lack sufficient RWA in occasional circumstances, elaborated further below, or when vPSG is not readily available. The fact that individuals with RBD are typically alert, coherent and oriented upon awakening (as is typical of REM sleep awakenings) is listed among the notes belonging to the diagnostic criteria but is not required as a criterion by itself, because this would naturally make a diagnostic awakening obligatory. It should also be noted that medication-induced RBD can be diagnosed as RBD according to current criteria.

18.3.2 RBD Diagnostic Criteria in DSM-5

The DSM-5 [12] criteria are presented in Table 18.3. It becomes evident that in the DSM-5 diagnostic manual used in psychiatry, there is a major difference with the classic ICSD-3 criteria, as it is stated that a diagnosis of RBD can be made based on a suggestive history without PSG documentation in patients in whom an α-synuclein disease has been diagnosed. On the one hand, it is in fact true that an established diagnosis of Parkinson's disease (PD), multiple system atrophy or dementia with Lewy bodies makes a diagnosis of RBD significantly more probable, if the typical behavioral or PSG signs of RBD are present, based on the simple fact that RBD is so prevalent in these diseases**.** On the other hand, it needs to be emphasized that even with these disorders confounding conditions can exist as RBD mimics, namely, with sleep apnoea [13] and periodic leg movements [14] that remain undetected if PSG is not performed. Of note, the DSM-5 criteria speak about "repeated episodes of arousal" [12] where RBD jerks and behaviors can occur without arousal and arousal could be seen as a consequence of impact or injury during "dream enactment" behaviors.

18.4 Strengths and Drawbacks of the Current Criteria

Some investigators have raised the question of whether there should be a minimal duration of REM sleep in a PSG recording to allow for or rule out a diagnosis of RBD, and this is mentioned as an open question in the ICSD-3 [1]. In the opinion of

the authors, if such a minimal duration criterion is introduced, it might probably be short. As in most cases with typical RBD, the relative amount of RWA in the EMG [15–18] and the number of behavioral episodes in the video [19–21] are high, so that few minutes would be expected to suffice. Nevertheless, other experts recommend a minimum REM sleep duration of 10% of total sleep time to be on the safe side to diagnose RBD, and in case of shorter REM duration, a second vPSG should be performed. Some authors have even suggested that in very selected difficult cases with advanced neurodegeneration, where EEG during PSG recording is often seriously altered and PSG also poses a high technical challenge, a typical appearance of RWA and behavioral jerking or episodes are so diagnostic for RBD that REM sleep per se can be recognized on this basis and RBD can be confidently diagnosed [22].

Another problem in the diagnosis of RBD according to ICSD-3 may be the lack of sufficient RWA in patients with otherwise clear RBD. One way to overcome this is using, in addition to EMG of the muscle mentalis, EMG recording of the upper extremities, as suggested by the Sleep Innsbruck Barcelona (SINBAR) group [15, 23]. The sensitivity of the extended montage including the upper extremities is considerably higher (91.8%), as compared to muscle mentalis alone (81.6%) [3]. The SINBAR montage is mentioned in the ICSD-3, but recording of the upper extremities is not yet obligatory for diagnosis of RBD up to now.

18.5 Polysomnography in the Diagnosis of RBD

Among all the parasomnias, RBD is the only one that mandatorily requires PSG for a definite diagnosis.

Since the first description of RBD in humans by Schenck and Mahowald [5], multiple studies have reported specific PSG characteristics. Chapter 20 is devoted to video-PSG findings in RBD, which can be subdivided into PSG (EEG, EMG, electrooculography, etc.) as well as videographic findings, and can be subject to visual and automatic analysis. Novel machine learning-based techniques are in development and presented in this chapter.

18.5.1 EMG in the Diagnosis of RBD

The different EMG methods which are currently used for the scoring of EMG activity in the diagnosis of RBD are explained in Chap. 31, which provides an overview and review of manual and computerized scoring methods. Manual scoring methods based on visual analysis have been demonstrated to provide a reliable basis for quantification of abnormal EMG activity, and different methods have been validated [24]. However, manual scoring of RWA is very time-consuming and can only be performed by highly skilled raters. For this reason, automatic scoring softwares have been developed [18, 25–27]. One of these systems can automatically score the upper extremities, in addition to the mentalis and submentalis muscles [27]. An overview of the computer-based automatic scoring of RWA is given in Chap. 31.

At present, however, this specific automatic analysis is available as integrated software only within the PSG system of one manufacturer [27]. Given the importance of an early and reliable diagnosis of RBD, and the complications of time-consuming manual EMG quantification, it can be expected that not only the analysis of the REM atonia index and the SINBAR automatic analysis programs will be used [28] and further developed, but also other programs, based on EMG or other neurophysiological signals, will be probably developed in the future.

18.5.2 Video and Other Recordings of Movement and Sound

In Chap. 21, Valerie Cochen De Cock provides a detailed overview of the current status of video studies in RBD and what their findings may implicate for the pathophysiology of RBD. Apart from the phenomenological aspect outlined in Chap. 21, movements and vocalizations may soon gain importance as diagnostic instruments for RBD [8].

The characteristic feature of RBD is not only the appearance of elaborate, complex, often violent and apparently dream-enacting behaviors, which have drawn clinicians' and investigators' attention since the beginning [29], but also the much more frequent elementary and minor extremity and body jerks, which are continuously present during REM sleep [19, 20, 30, 31] as a manifestation of "background jerking" [8].

In addition to quantification of increased EMG activity, these jerks are another hallmark of RBD, and their potential as an objective treatment outcome measure remains to be investigated [8].

High-quality video monitoring could be one method to detect these jerks, and the suitability of other methods (e.g. actigraphy) remains to be established [32].

Vocalizations may prove to provide the basis for additional diagnostic tools for RBD [33–35]. In difference to regular sleep talking, the hallmark of RBD-related vocalizations is the large variability of vocalizations, including intense emotionality, as found with loud swearing and angry phrases.

18.6 Reconciling the Terminology in RBD

This paragraph deals with a new designation of "isolated RBD" [8], which has been suggested to replace the former terms idiopathic RBD or cryptogenic RBD [8, 36], and with the new concept of "prodromal RBD" for which clear diagnostic criteria have been defined and which now can be distinguished from isolated RWA.

Historically, the presence of RBD alone in the absence of any comorbid neurodegenerative or other disease was called idiopathic RBD, but increasing research has made clear that a very large proportion of these patients will develop α-synuclein disease in the subsequent years and that in the stage of "idiopathic" RBD slight abnormalities of waking EEG, cognitive function, motor function, olfactory and visual function and others can be found [8, 37, 38] (see also Chap. 36 by Ron

Postuma). Therefore, more than 10 years ago Ferini-Strambi et al. suggested to replace the term idiopathic RBD with cryptogenic RBD [36].

In the past decade, considerable research advances have been made, and it has become clear that even in patients with very long-standing (more than 10 years) persistent "idiopathic" RBD, when they are examined in detail, other biomarkers of α-synuclein disease can be found, which means that in these patients, despite still having idiopathic RBD, manifest neurodegeneration is nevertheless present [39].

On the basis of this evidence, it has been suggested by Högl, Stefani and Videnovic in early 2018 [8] that the designation of RBD should be changed from idiopathic RBD or cryptogenic RBD to "isolated RBD" (iRBD) [8], reflecting the current stage of research more accurately, while not causing any change in abbreviation, viz. iRBD remains iRBD. This change in designation is fully justified because underlying α-synuclein pathology has been clearly demonstrated in multiple in vivo and postmortem studies of iRBD, and so there is virtually no bona fide case of idiopathic RBD.

18.7 The Concept of Prodromal RBD

Sixel-Döring and the Kassel Group [9, 21] have first observed short and often minor video events, called REM behavioral events (RBE), in healthy persons or PD patients who did not yet fulfil the criteria of full-blown RBD [21], but subsequently developed full-blown RBD, and suggested the term prodromal RBD [9]. Based on EMG analysis, the Innsbruck Group showed that even REM sleep without atonia increases over time [10] and some of the patients who are above EMG thresholds for RBD diagnosis without meeting other RBD diagnostic criteria [40] will develop RBD in subsequent years [10].

Therefore the concept of prodromal RBD, based on video (≥2 REM behavioral events) and EMG (>32% of 3 s REM mini-epochs having any chin or phasic flexor digitorum superficialis activity), is now a solid concept based on two different pathways [8], as shown in Fig. 18.1 [8], and potentially very useful for future symptomatic or disease-modifying studies in RBD.

18.8 Questionnaires for RBD

A series of several specific questionnaires have been developed to screen for RBD. Their advantages and limitations are presented in detail in Chap. 19, by the Wing group. Questionnaires may be used to make a provisional diagnosis of RBD. PSG demonstration of RWA and any type of documentation of abnormal behaviors is necessary for the definite diagnosis or RBD, whereas questionnaires can only be used to make a diagnosis of probable RBD. Although most questionnaires showed excellent clinometric properties in their respective validation studies (see Chap. 19), subsequent use outside the strict context of validation studies has shown that the results are far less good and often problematic, and false positives

and false negatives occur [8]. This has been recently confirmed in patients with da novo Parkinson's diesase, wiht an AUC of 0.68 [41], as well as in the elderly Spanish community, with a positive predictive value of the used validated questionnaire of only 25% [42]. Therefore, the current role of questionnaires is seen as first screening step in a multistep procedure [43].

Conclusions

In summary, the importance of a correct diagnosis of RBD cannot be overemphasized, due to its implications for the individual patient with respect to the high risk for future emergence of neurodegenerative disease and also with respect for neuroprotective or disease-modifying treatment trials. While in past years it has become common knowledge that questionnaires alone are not suitable for RBD diagnosis, ongoing research is trying to identify screening methods for RBD [8]. Whether or not the diagnosis of RBD can be obtained in the future without PSG, perhaps based on novel technologies, remains to be established. At present, the diagnostic gold standard is PSG, including high-quality EMG recording from chin and upper extremity muscles.

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Instruments for Screening, Diagnosis and Assessment of RBD Severity and Monitoring Treatment Outcome

19

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19.1 Introduction

REM sleep behavior disorder (RBD) is a distinct parasomnia associated with a loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep and characterised by motor activity in response to vivid, often unpleasant, and violent dreams. Patients with RBD may exhibit a repertoire of behavioral manifestations during sleep, ranging from simple acts, such as moaning, sleep talking and shouting, to vigorous and elaborate motor activities, such as punching, kicking, gesturing and even jumping from bed. Sleep-related injuries to self and to bed partner are therefore common sequelae (e.g. bruises, fractures) and may often be the initial reason for seeking medical consultation [1]. Because of these disruptive, often action-packed sleep behaviors, RBD can cause increased distress in the patient's partner/spouse [2] and can even result in potentially lethal behaviors with forensic implications and consequences [3]. Idiopathic RBD (iRBD) has been identified as an early precursor of α-synucleinopathy, such as Parkinson disease (PD) and dementia with Lewy bodies (DLB). Longitudinal studies have consistently found that over 70–80% of patients with iRBD eventually developed synucleinopathy neurodegeneration in 10–15 years [4, 5]. The strong link between RBD and neurodegeneration has opened up an important new avenue for searching for promising neuroprotective agents and designing research strategies to halt the progression towards overt neurodegeneration [6]. As such, early detection and the timely, accurate diagnosis of RBD are of paramount importance.

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To ascertain the diagnosis of RBD, video-polysomnography (vPSG) remains the gold standard. Nonetheless, PSG is resource-intensive and time-consuming and requires specialised training. It is not widely accessible and is impractical for screening large numbers of individuals. Thus, there is a need for simpler instruments, such as questionnaires, to help elicit symptoms of RBD for the purpose of screening and for an initial presumptive diagnosis of RBD for use in resource-constrained clinical settings and large-scale research studies. In addition, the clinical presentation of RBD and dream enactment behaviors may vary with an episodic nature, and the behavioral manifestations may not be fully captured during overnight vPSG [7], and so there is a need for instruments that allow for assessing the severity of RBD and monitoring treatment progress over time.

Physicians and researchers are faced with an important decision of selecting an appropriate and suitable RBD scale for their clinical and research use. Choosing a diagnostic instrument requires a thorough understanding of the context of the test's validation procedure and psychometric properties of the scales (e.g. validity, reliability). The optimal design for assessing a test's utility is an independent, blind comparison of the test and an appropriate reference standard (in the case of assessing RBD, PSG is considered as the gold standard) in a consecutive series of patients from a relevant clinical population [8]. Several psychometric properties are often examined when evaluating the diagnostic accuracy of a test. Validity is one of the fundamental psychometric concepts, which refers to the extent to which a test measures what it is intended to measure. It is reflected by the test's sensitivity and specificity. *Sensitivity* refers to how well a test can identify those with the disease condition (RBD) whereas *specificity* is the ability of a test to correctly identify those without the disease condition. In addition, two other relevant terms are useful for clinicians to consider regarding the value of the test: *positive predictive value (PPV)* is the probability that the patient has the disease condition when the test result is shown to be positive, and *negative predictive value (NPV)* is the probability that the patient does not have the disease condition given a negative test result.

Several instruments have been developed in the past several years for the use of screening RBD and monitoring symptom severity of the patients already diagnosed with RBD. Their properties, limitations and utility in clinical and research settings are reviewed and discussed in this chapter.

19.2 REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)

RBDSQ is a self-administered instrument designed as a RBD screening tool. It consists of 10 items with 13 questions to assess various clinical features of RBD, including dream features, nocturnal motor activities, sleep-related injuries, nocturnal awakenings, sleep disturbance and presence of any neurological disorder [9]. To enhance its diagnostic accuracy, input of the bed partner is generally recommended when completing the RBDSQ. Responses to RBDSQ are given as binary (yes/no) items based on the lifetime occurrence of these RBD features. The total score ranges

from 0 to 13. According to the original validation study, a cut-off score of 5 is suggestive of the presence of RBD [9]. The diagnostic capacity of RBDSQ was initially evaluated in PSG-confirmed RBD patients and two control groups: (1) subjects recruited from a sleep clinic with the diagnosis ascertained by history and PSG and (2) healthy subjects recruited from the community in which RBD diagnosis was excluded by medical history only and without PSG confirmation. RBDQSQ demonstrated a good internal consistency (Cronbach's alpha = 0.89) and a reasonable discriminatory capacity to differentiate RBD patients from controls with an AUC of 0.87 ± 0.38, showing 96% sensitivity and 56% specificity at the suggested cut-off of 5. The relatively lower sensitivity was possibly explained by the inclusion of control patients with different sleep disorders in the study, such as non-REM parasomnias and obstructive sleep apnoea (OSA). When evaluating RBDSQ using the control subjects recruited from the general population (those not presenting to a sleep clinic), the scale yielded a much higher specificity (92%), with 93% correct diagnosis [9].

The original RBDSQ was published in German and English [9]. RBDSQ has been subsequently translated and validated in other languages, including Japanese [10], Chinese [11], Korean [12], and Italian [13]. The validation studies conducted in Japan and China reported that the original cut-off at a score of 5 showed a comparable capacity of differentiating RBD patients from control subjects with other sleep disorders and healthy normal subjects. The Italian version of RBDSQ was validated in 76 RBD patients and 304 patients with other sleep disorders who had been assessed by PSG, as well as 101 healthy control subjects who underwent only a clinical assessment (without PSG confirmation) to exclude the presence of any sleep disorder or other clinical conditions. The Italian version of RBDSQ was slightly modified with a cut-off score suggested to be higher (RBDSQ score of 8). As item 10 in the original RBDSQ (presence of any neurological disorder) is related to an etiological assumption about RBD, i.e. its association with neurological diseases, the removal of item 10 in the original RBDSQ was found to yield a better discriminatory power (AUC, 0.899; sensitivity, 82.9%; specificity, 82.0%) in this study [13]. The suggestion of removing item 10 is also supported by the observations that RBD could be present in other clinical populations, including those with narcolepsy and also younger and female psychiatric patients [14, 15]. The diagnostic accuracy of the Korean version of RBDSQ (RBDSQ-K) was tested and compared among three groups: patients with PSG-confirmed RBD (n = 47), untreated OSA patients assessed by PSG (n = 213) and healthy controls in which sleep diagnoses were excluded by medical history (n = 58) [12]. The suggested optimal cut-off was higher for distinguishing RBD patients from those with OSA (score of 6.5) than for differentiating RBD patients from healthy controls (score of 4.5). Although the apnoea-hypopnea index was not found to be correlated with RBDSQ-K score, OSA patients with daytime sleepiness (Epworth Sleepiness Scale, ESS score ≥ 10) scored significantly higher on the RBDSQ-K than those without daytime sleepiness, which suggested the need for clinicians to be mindful of the possibility of false positives when using the scale, especially among OSA patients.

RBDSQ has been tested and utilised to examine the prevalence of probable RBD in the general population [16, 17]. In the study conducted among the residents of a

rural community in Japan, Nomura et al. reported that a score of 6 on the RBDSQ represented the best cut-off for screening RBD in the general population (sensitivity, 100%; specificity, 73.0%), albeit that the RBD diagnosis in this study was based on a telephone interview only [17]. The utility of RBDSQ has also been examined in patients with PD [11, 18, 19]. A higher total score of six has been suggested as the optimal cut-off value for detecting RBD in patients with PD [11, 19]. When testing RBDSQ in patients with PD, Stiasny-Kolster and colleagues showed that the sensitivity and specificity of the questionnaire also depended on the circumstances of its application (e.g. whether the patients had received a thorough evaluation, including taking a sleep history about RBD, and also an explanation prior to completing the questionnaire) [18]. Moreover, Stefani and colleagues investigated the diagnosis of probable RBD in a 2-year longitudinal epidemiological study in the elderly population. They found that the consistency between the two assessments conducted 2 years apart using RBDSQ was low (correlation coefficient *r*, 0.35; intraclass correlation coefficient, 0.39) [20]. Whilst the fluctuation of symptoms in untreated RBD may be a possible explanation for such a low agreement, their findings nonetheless suggested the need of caution in interpreting the questionnaire-based RBD diagnosis.

19.3 REM Sleep Behavior Questionnaire (RBDQ-HK)

RBDQ-HK is a self-report measure of RBD symptoms that can be utilised for clinical screening and treatment monitoring. It can be completed by the patient whilst the input of bed partner is always encouraged. RBDQ-HK consists of 13 items designed to assess various symptoms that correspond to two essential clinical aspects of RBD—dream-related features and behavioral manifestation. Each item is rated on two scales—lifetime occurrence and recent 1-year frequency. Respondents are asked to indicate whether they have experienced the symptoms in their lifetime (no/don't know = 0, yes = 1) and the frequency of the symptoms over the past year (none = 0, once or few times a year = 1, once or few times a month = 2, once or twice a week = 3, at least three times a week = 4). The scores of items 6–12 (sleep talking, sleep shouting, dream-related movements, falling out of bed, attempt to assault/injure, sleep related injury [SRI], SRI related to dream content) were additionally weighted (doubled) to address the clinical importance of the behavioral aspects of RBD. The total RBDQ-HK score is calculated by adding up the scores from the lifetime and recent 1-year scales, with a range from 0 to 100.

The original validation study of RBDQ-HK involved a mix of clinical and community-based samples: PSG-confirmed RBD patients ($n = 107$) and control subjects ($n = 107$) including patients referred to the sleep clinic for various sleep complaints, patients recruited from the psychiatric clinic and healthy normal subjects recruited from the community. The diagnoses of all the subjects in the original validation study were independently ascertained by clinical interview and PSG. The questionnaire was shown to have satisfactory psychometric properties, including good internal consistency (Cronbach's alpha coefficient: 0.9 for the overall scale, 0.86 and

0.86 for dream-related and behavioral factors, respectively) and test-retest reliability (0.89 and 0.80 for the lifetime and recent 1-year frequency scales, respectively). Optimal cut-off of the RBDQ-HK was 18/19, which yielded a sensitivity of 82.2%, a specificity of 86.9%, a negative predictive value of 86.3% and a positive predictive value of 83.0% [21]. It has been suggested that the seven items corresponding to the behavioral factor of the RBDQ-HK could be taken out and used separately for screening purpose, with a diagnostic capacity comparable to that of the full RBDQ-HK scale (best cut-off at 7/8: sensitivity, 87.9%; specificity, 81.3%; PPV, 82.5%; NPV, 87.0%). RBDQ-HK has been further validated in Japan (RBDQ-JP) [22], mainland China [23] and Korea (RBDQ-KR) [24], showing comparable, satisfactory psychometric properties as a screening tool. It was also being used in a large-scale community-based study (n = 12,784 Chinese adults, aged 24 or older) to examine the prevalence of probable RBD (pRBD) and the risk factors associated with pRBD [25].

Apart from screening and diagnostic purposes, the RBDQ-HK has been used for monitoring symptomatic treatment of RBD. In a study that investigated the treatment effectiveness (pramipexole monotherapy, clonazepam monotherapy or combined pramipexole and clonazepam) in 45 RBD patients, the RBDQ-JP score (Japanese version of the RBDQ-HK), particularly for the frequency scale, showed a significant reduction after the treatment. The change of RBDQ-JP score upon pharmacological treatment was also significantly correlated with the clinical global impression (CGI) improvement score (r, −0.83; $p < .001$), which suggested the scale's sensitivity to the change of symptoms and its utility of monitoring symptomatic treatment of RBD. To increase its sensitivity to monitor treatment progress over a short period of time, the frequency subscale and the timeframe of the RBDQ-HK have been further modified [26]. In this revised version of the RBDQ-HK, i.e. RBDQ-3M, respondents are asked to indicate the frequency of the symptoms in the past 3-month period. Each item is scored on a four-point scale (none, less than once a month, once or twice a month, at least once a week). The total RBDQ-3M score ranges from 0 to 60. RBDQ-3M has been shown to correlate well with the original RBDQ-HK (overall scale: $r = 0.96, p < .001$; dream-related factor: $r = 0.98, p < .001$; behavioral factor: r = 0.96, $p < .001$). RBDQ-3M has been used in a prospective treatment study that investigated the clinical changes in response to clonazepam treatment in RBD patients [26]. The severity of clinical RBD symptoms as measured by RBDQ-3M was shown to be significantly improved upon treatment with a large effect size (Cohen's d = 0.74–0.9) [26].

19.4 Mayo Sleep Questionnaire (MSQ)

Mayo sleep questionnaire (MSQ) consists of 16 items designed to screen for the presence of a wide range of sleep disorders (e.g. RBD, PLMS, RLS) [27]. Unlike most other developed scales, MSQ is designed to be completed by caregivers/bed partners. The presence of RBD is assessed by a single question focusing on recurrent dream enactment behavior: 'Have you ever seen the patient appear to "act out

his/her dream" while sleeping? (punched or flailed arms in the air, shouted or screamed)'. Five additional questions are subsequently asked when the initial response is positive. MSQ was initially validated in 176 aged participants (median age, 71 years; male, 85%) assessed by PSG, with the majority (96%) having cognitive impairment and/or parkinsonism due to an underlying neurodegenerative disorder and a few (4%) as healthy controls. The single core MSQ question on RBD showed a sensitivity of 98% and specificity of 74% for the diagnosis of RBD in the aged cognitively impaired patients [27]. MSQ was further validated in a sample of community-dwelling elderly (median age, 77 years; male, 89%), consistently showing good psychometric properties (sensitivity, 100%; specificity, 95%) [28]. MSQ is a simple instrument with high sensitivity. Nonetheless, a practical constraint is the need for input from the bed partner, which may not be always available especially for those aged patients.

19.5 RBD1Q

The RBD1Q comprises one single self-administered question that can be answered with a 'yes' or 'no' response: 'Have you ever been told, or suspected yourself that you seem to "act out your dreams" while asleep (e.g. punching, flailing your arms in the air, making running movements, etc.)?' This question was translated into French, German, Japanese, Italian, Spanish, Czech and Danish and was validated at 12 centres of the International REM Sleep Behavior Disorder Study Group [29]. The validation study involved 241 idiopathic RBD (iRBD) patients and 242 controls (patients with other sleep disorders and healthy controls) who underwent PSG assessment to ascertain their diagnosis. RBD1Q was shown to have good sensitivity (94%) and specificity (87%) in diagnosing RBD. Subgroup analysis also suggested that RBD1Q has adequate specificity (92.2%) when tested in patients with OSA. However, its capability of discriminating non-REM parasomnias from RBD remains unclear. Given its simple design and cross-cultural validation, RBD1Q may be considered a good screening tool in clinical settings and large-scale epidemiological studies.

Although RBD1Q showed good diagnostic capacity when being used in the setting of sleep centres, a recent study conducted in the general elderly population found only a low positive predictive value of the RBD1Q (25%), based on a two-stage study design with video-polysomnographic confirmation of RBD diagnosis at the second stage [30]. In another community-based study, RBD1Q was translated into Chinese with a slight modification to examine the prevalence of probable RBD (based on RBD1Q only without PSG confirmation) and its association with PD [31]. This modified version of RBD1Q additionally took into account sleep-related vocalisations during RBD episodes: 'Do you have the following conditions (or have you ever been told by your husband or wife) that you *shout, yell,* move your arms or legs in response to your dream contents, even fallen off your bed?' The modified version was validated against PSG and clinical history in a small sample (14 iRBD

patients and 18 controls), showing high sensitivity (100%) and negative predictive value (NPV, 100%) but modest specificity (55.6%) and positive predictive value (PPV, 63.5%). Based on this modified version of RBD1Q, the prevalence of probable RBD (pRBD, diagnosed without PSG confirmation) was estimated to be 4.9% (95% CI: 4.6–5.1%), increasing with age and with a peak in those aged 70–79 years. Surprisingly, the estimated prevalence of pRBD was found to be higher in women (female vs. male: 5.6% vs. 4.1%, $p < .001$). In addition, it was found that the prevalence of PD was significantly higher in those with pRBD than those without pRBD (1.2% vs. 0.4%, age- and sex-adjusted *or* = 2.61, 95% CI: 1.56–4.39, $p < 0.001$).

19.6 Innsbruck Sleep Behavior Disorder Inventory (RBD-I)

RBD-I is a five-item instrument designed to screen for the presence of RBD. The original scale was designed and validated in the German language and was translated into English [32]. In the initial validation process, similar to RBDQ-HK, RBD-I was designed with two parts to assess the presence and frequency of RBD symptoms, respectively. The first part of RBD-I asks about the presence of five aspects of RBD symptoms (violent/aggressive dream content, sleep-related vocalisations, sleep-related extensive movements, sleep-related injurious behaviors and dream-behavior isomorphism), and the responses can be given as 'yes', 'no' or 'don't know'. RBD symptom score is calculated by dividing the number of positive responses (yes) by the number of answered items. The total RBD symptom scores range from 0 (minimum) to 1 (maximum). The second part of RBD-I is designed to assess the frequency of symptoms in the past year with the following response options: never = 0, rare (once to a few times per year) = 1, occasional (once to a few times per month) = 2, frequent (1–2 times per week) = 3 and very frequent (more than 2 times per week) = 4. RBD frequency score is calculated by dividing the number of answered items by the total number of items, with a possible score ranging from 0 (minimum) to 4 (maximum).

RBD-I was initially validated in 70 idiopathic and symptomatic RBD patients and 140 patients with other sleep disorders (e.g. sleep-related breathing disorder, restless legs syndrome, insomnia, non-REM parasomnias) recruited from a sleep laboratory [32]. The sleep diagnoses of all the participants were ascertained by both clinical history and PSG assessment in this study. The RBD symptom score of RBD-I showed satisfactory sensitivity (0.914) and sensitivity (0.857) at a cut-off of 0.25. As the diagnostic capacity of the overall scale was not further enhanced by taking into account the RBD frequency score, it was suggested by the authors that asking the presence of the symptoms alone could be sufficient to distinguish RBD and non-RBD cases. Moreover, it was proposed that the item on dream enactment in RBD-I ('Do you kick or hit during your sleep because you dream that you have to defend yourself?' Answer: yes or no) could be used alone for screening purpose in large-scale population-based studies. Nonetheless, this single item yielded only moderate sensitivity (0.743) and comparatively high specificity (0.929).

19.7 REM Sleep Behavior Disorder Severity Scale (RBDSS)

Unlike other scales that can be directly self-administered or completed by bed partner/caregiver in clinical settings and epidemiological studies, RBDSS is a rating scale developed for scoring the severity of RBD symptoms during video-PSG [33]. Motor events during REM sleep are rated from 0 to 3 based on the localization and severity of movements: '0 = no visible motor activity, REM sleep without atonia present; 1 = small movements or jerks; 2 = proximal movements including violent behavior; 3 = axial movements including bed falls'. Vocalisations during REM sleep are scored as either 0 (absent) or 1 (present). The final RBD severity score is determined by the highest score given in at least one REM episode, i.e. the most severe episode during PSG recording. It was found that PD patients exhibited significant night-to-night variability in their RBD symptoms based on the ratings of the scale assessed across two consecutive nights of video-PSG recording [33]. In an open-label trial of Ramelteon conducted in 12 iRBD patients, RBDSS was used to examine the treatment effect [34]. Whilst there was a trend towards significance in the visual analogue scale (VAS) designed to measure daily clinical symptom severity in this study, no significant difference was found in the RBDSS score before and after the intervention (at least 4 weeks of 8 mg Ramelteon given within 30 min before bedtime).

19.8 Structured Diagnostic Interview for Sleep Patterns and Disorders (DISP)

The Structured Diagnostic Interview for Sleep Patterns and Disorders (DISP) was developed by the National Institutes of Health Intramural Research Program in collaboration with two sleep specialty clinics, the Stanford Center for Sleep Science and Medicine and the Center for Sleep and Wake Disorders. It was designed to establish the diagnosis of various sleep disorders according to the diagnostic criteria in the *International Classification of Sleep Disorders*, second edition (ICSD-2) [35]. The DISP, which consists of several modules to assess sleep-wake patterns and a wide range of sleep disorders, can be administered as either face-to-face or telephone interview by trained lay persons. The section on RBD in the DISP has four initial screening questions (i.e. self-report of 'acting out' thoughts in dreams, dream enactment behaviors reported by others, disruption of sleep by these movements and sleep-related injury). If the participant responds positive to any of these questions, a more comprehensive evaluation will be subsequently conducted with follow-up questions to collect more detailed information of RBD (e.g. duration, course and episodes including onset and offset history, associated impairment and severity and history of help seeking and treatment). The preliminary validation and evaluation study showed that DISP could reasonably differentiate RBD cases with high specificity (0.96) but modest sensitivity (0.50) and overall accuracy of 0.94 [35]. The DISP can help to establish a comprehensive profile of the clinical presentation of RBD other than assessing its symptom severity. Whilst DISP has a highly structured format that can be administered by trained personnel, the interrater reliability

and test-retest reliability have not been clearly established in the initial validation study. Similar to other scales, as the validation was conducted in patients referred to the sleep centres, the psychometric properties of DISP are yet to be tested in the community-based samples.

19.9 Summary

19.9.1 Considerations of Using RBD Instruments for Screening and Diagnostic Purposes

Several RBD instruments have been developed in the recent years, and generally have satisfactory psychometric properties (Table 19.1). These RBD instruments were initially tested in RBD patients who were followed up in a sleep clinic and their respective controls. As such, RBD patients included in these initial validation studies may be more knowledgeable about their condition and may have a more severe clinical presentation that required medical attention. A previous study conducted in PD patients has shown a much lower sensitivity and specificity of the same scale (RBDSQ) when being administered during routine work-up (sensitivity: 0.68, specificity: 0.63) as compared to being tested in those who have been previously assessed by clinical interview about their RBD condition (sensitivity: 0.90, specificity: 0.87) [18]. The core RBD question from MSQ has shown lower PPV (69.2%) when tested in the community as compared to being administered in clinical samples (82.3%) [27, 28]. Clinicians and researchers should therefore be mindful that the psychometric properties (e.g. sensitivity, specificity) and optimal cut-off of these instruments may vary when being used in different settings or populations (e.g. RBD in another context, such as psychiatric disorders and narcolepsy, community-based samples, patients with PD) [11, 17, 19].

Whilst most existing RBD questionnaires are primarily designed to be self-administered, input from spouses/caregivers are always encouraged because patients themselves may not be able to recall their dream content or be fully aware of their nocturnal sleep behavior. In a recent study of the largest cohort of iRBD patients reported to date involving 203 consecutive patients, 44% were found to be unaware of their dream-enacting behaviors, which were only reported by the spouse [36]. Also, patients may have concomitant cognitive difficulties that could limit their ability to report their symptoms. It is also important to keep in mind that a screening test is not meant to be fully diagnostic. The use of the validated questionnaires may facilitate identifying and prioritising those high-risk individuals who may need timely assessment and intervention. Nonetheless, the clinical presentation of RBD may be mimicked by severe OSA [37] and severe periodic limb movements [38] or may overlap with that of NREM parasomnias, which could be overlooked and could not be clearly differentiated by the self-administered instruments. A referral to sleep specialists for further and more definitive examination with clinical interview and video-PSG is recommended in clinical practice for individuals who are suspected to have RBD based on the result of the selected instrument.

Table 19.1 Characteristics of the validated instruments to assess REM sleep behavior disorder (RBD)

	RBDQSQ	RBDQ-HK	MSQ	RBD1Q	RBD-I	RBDSS	DISP
No. of items	13	13	1 screening item (followed by 5 additional items if positive)	1	5	2	4 screening items (followed by more detailed questions if positive)
Translations	English, German, Japanese, Chinese	English, Chinese (traditional/ simplified), Japanese	English	English, French, German, Japanese, Italian, Spanish, Czech, Danish	English, German	English	English, Chinese
Validated population	Clinical	Clinical	Clinical, community	Clinical	Clinical	Clinical	Clinical
Response option	Yes/no	1. Lifetime scale: yes/no/ don't know 2. Frequency scale	Yes/no	Yes/no	1. Symptom score: yes/ no/don't know 2. Frequency score	Phenomenological categories (0–3)	1. Screening items: yes/no/ unknown 2. Follow-up item: different response options, e.g. duration
Face validity	✓	✓	✓	✓	✓	✓	✓
Internal consistency (Cronbach's alpha)	0.89[a]	0.90[b]	–	–	0.86	–	–

Test-retest reliability	–	0.80–0.89[b]	–		–	–	–	–
Criterion validity			Sleep centre	Community				
Sensitivity %	96.0 [a]	82.2[b]	97.5[c]	100[d]	93.8[e]	91.4[f]	–	50.0%[g]
Specificity %	56.0 [a]	86.9[b]	74.2[c]	95.5[d]	87.2[e]	85.7[f]	–	96.0%[g]
PPV %	66.0 [a]	86.3[b]	82.3[c]	69.2[d]	87.9[e]	76.0[f]	–	–
NPV%	–	83.0[b]	96.1[c]	100[d]	93.4[e]	95.0[f]	–	–
AUC	0.87[a]	0.90[b]	–	–	–	0.89[f]	–	0.73[g]

Notes: Modified from Lam et al. Sleep Medicine 2013

Abbreviations: *RBDSQ* REM sleep behavior disorder screening questionnaire, *RBDQ-HK* REM sleep behavior questionnaire-Hong Kong, *MSQ* Mayo sleep questionnaire, *RBD-I* Innsbruck sleep behavior inventory, *RBDSS* REM sleep behavior disorder severity scale, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the curve

[a]Stiasny-Kolster et al. [9]

[b]Li et al. [21]

[c]Boeve et al. [27]

[d]Boeve et al. [28]

[e]Postuma et al. [29]

[f]Frauscher et al. [32]

[g]Merikangas et al. [35]

19.9.2 Choosing RBD Instruments for Different Purposes: Which One to Use?

The suggested utility of different RBD instruments is summarised in Table 19.2. Whilst the majority of RBD instruments can be used for screening purpose, the simple one-item design of MSQ and RBD1Q renders an advantage of their utility in large-scale epidemiological studies. Meanwhile, RBDQ-HK and its modified version (RBDQ-3M), RBD-I, and RBDSS may be suitable for assessing RBD symptom severity and monitoring treatment response as well as disease progress because they provide a quantitative measure that allows for a comparison of symptom severity over time. Although RBDSS can be used to rate the severity of RBD, it is limited by its use for assessing motor events during video-PSG, whereas other scales (RBDQ-HK, RBDQ-3M, RBD-I) can be readily used in clinical or research settings where PSG is not available. In particular, the modified version of RBDQ-HK, i.e. RBDQ-3M, has been shown to be a valid and sensitive measure to detect changes in response to treatment over time in RBD patients [26].

19.9.3 Future Research Directions and Conclusions

The development of RBD instruments has substantially facilitated research on the epidemiology of RBD, with growing studies utilising the available RBD instruments to examine the prevalence and risk factors of RBD in the general and clinical populations. Although the existing RBD instruments may have their unique strengths, with cultural and linguistic adaptations where needed, a lack of a unified

Table 19.2 Utility of different RBD instruments in clinical and research settings

	RBDQSQ	RBDQ-HK	RBDQ-3M	MSQ	RBD1Q	RBD-I	RBDSS	DISP
Quick screening				✓	✓			
Initial diagnosis	✓	✓		✓	✓	✓		✓
RBD symptom profiling		✓	✓			✓	✓	✓
Assessing symptom severity		✓	✓			✓	✓	✓
Monitoring treatment response		✓	✓			✓	✓	
Monitoring disease progress		✓	✓			✓	✓	

Notes: Modified from Lam et al. Sleep Medicine 2013
Abbreviations: *RBDSQ* REM sleep behavior disorder screening questionnaire, *RBDQ-HK* REM sleep behavior questionnaire-Hong Kong, *RBDQ-3M* modified REM sleep behavior questionnaire-Hong Kong, *MSQ* Mayo sleep questionnaire, *RBD-I* Innsbruck sleep behavior inventory, *RBDSS* REM sleep behavior disorder severity scale, *DISP* Diagnostic Interview for Sleep Patterns and Disorders

RBD instrument may hinder a direct comparison of the results across the studies. For example, a recent population-based study reported slightly variable prevalence rates of probable RBD when using RBDSQ and RBD-I: 4.6% as assessed by RBDSQ vs. 7.7% as assessed by RBD-I [16]. Moreover, only few RBD scales (e.g. RBDQ-HK, RBDQ-3M, RBD-I frequency score) have been developed for the use of monitoring symptom severity, which is important for devising future randomised controlled trials of RBD treatment and neuroprotective agents for the prevention of overt neurodegeneration [6].

Note Added in Proof: The following is an additional pertinent publication: (1) Nomura T, Tanaka K, Tajiri Y, Kishi M, Nakashima K. Screening tools for clinical characteristics of probable REM sleep behavior disorder in patients with Parkinson's disease. eNeurological Sci. 2016;4:22–4. Also, recent evidence suggests that actigraphy can be another useful screening tool for RBD: (2) Stefani A, Heidbreder A, Brandauer E, et al. Screening for idiopathic REM sleep behavior disorder: usefulness of actigraphy. Sleep. 2018 Jun 1;41(6). doi: 10.1093/sleep/zsy053.

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Selective Polysomnographic Findings in REM Sleep Behavior Disorder (RBD) and Parkinson's Disease

20

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Polysomnography (PSG) constitutes the core method for identifying REM sleep behavior disorder (RBD) due to the lack of muscle atonia during REM sleep (REM sleep without muscle atonia—RSWA). Simultaneous documentation with video is central for identifying behavioral, verbal, and minor motor activity during sleep. RBD is related to alpha-synucleinopathies and constitutes a potential risk for conversion into parkinsonism including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), among others [1]. Furthermore RSWA and RBD are strongly associated with hypocretin-deficient narcolepsy [2] (narcolepsy with cataplexy, i.e., type I) and has furthermore been associated with structural brain stem lesions [3–5].

The underlying pathophysiology associated with electrophysiological changes in alpha-synucleinopathies comprises early and progressive involvement of brain stem and midbrain structures including the lower brain stem, pontine, hypothalamus, and thalamic areas consequently. Several sleep abnormalities have been described related to the involvement of these brain structures, and they consist of sleep-wake disturbances; sleep transitions; abnormal sleep structure, such as abnormalities in micro-sleep structure; and abnormal motor control in REM and NREM sleep [6]. Furthermore, impairment of autonomic regulation has been found during NREM and REM sleep as well as in wakefulness [7–10].

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An analysis of changes of electromyographic patterns during PSG of RBD patients is presented in Chap. 31, while Chap. 32 covers the autonomic dysfunction in RBD. In this chapter we primarily focus on other polysomnographic and electrophysiological abnormalities associated with RBD and early stages of synucleinopathy development.

20.1 Electroencephalographic Changes in RBD and PD

Patients with RBD and in particular parkinsonism have shown slowing of the electroencephalographic (EEG) spectra during wake and REM sleep phase. In particular, Fantini et al. were the first to observe that RBD patients during wakefulness are characterized by higher theta power in frontal, temporal, and occipital regions while lower beta power in the occipital region when compared to controls. During REM sleep, RBD patients were characterized by lower beta power in the occipital regions than controls [11]. A recent study by Rodrigues Brazète et al. has shown that during wakefulness, RBD is characterized by slowing in frontal, central, parietal, temporal, and occipital regions and that slowing was enhanced in RBD patients who later developed a synucleinopathy [12]. Iranzo et al. evaluated the spectral changes in RBD patients that later developed mild cognitive impairment (MCI), and they found increased delta and theta activity in the central region compared to the occipital one and also in the right hemisphere compared to the left one [13]. In addition, they observed that these patterns were enhanced in patients who later developed MCI. These results were also confirmed in later studies [14, 15]. Changes related to EEG spectral power during REM sleep in RBD have been used to successfully distinguish RBD from healthy controls with a data-driven machine learning technique reaching sensitivity and specificity of around 90% [16].

NREM sleep seems not to be affected by the same EEG slowing that has been observed in REM sleep and wakefulness. NREM EEG slow-wave features were extracted with an automated algorithm in a study by Latreille et al. [17], and EEG slow-wave density, amplitude, frequency, slope, and duration of positive and negative phases were similar in RBD patients and healthy controls.

The EEG slowing observed in RBD during REM sleep and wakefulness is consistent with the observations performed in the early stages of PD and DLB [18–20]. This phenomenon may be considered as an effect of the pathophysiological changes related to the disease, such as involvement of brain stem and thalamic structures that project to the cortex [21], cortical thinning, and white matter abnormalities [22, 23].

Recently, algorithmic complexity of spectrograms calculated from wakefulness resting EEG in RBD and healthy controls has been investigated by Ruffini et al. [24]. RBD patients that later developed PD and DLB showed decreased complexity of the EEG signals in both low and high frequencies. Another recent study has also shown that during wakefulness, RBD patients are characterized by a loss of delta-band functional connectivity [25].

20.2 Micro- and Macrostructural Sleep Changes in RBD and PD

Concerning microstructural changes observed in PD and RBD, some studies have focused on sleep spindles (SS). Christensen et al. have analyzed SS density and morphology in both manually and automatically identified SS: when the manual annotations were used, there was not any found association between PD disease duration or severity and SS density and morphology [26]. However, when an automated method for SS detection has been employed, it was found that in NREM sleep, RBD and PD patients (with and without RBD) were characterized by a significantly lower density of SS [27]. In another study, O'Reilly et al. confirmed the reduced density of SS in RBD, with the strongest effect in the central and parietal derivations. At the same time, they pointed out that it is important to differentiate between fast and slow SS: for the former, a decreased density is observed, while for the latter, the opposite was shown [28]. These results suggest a possible thalamic dysfunction in early stages of alpha-synucleinopathies. In another study by Latreille et al. [15], it was observed that PD patients who later converted to dementia were characterized by lower SS density and amplitude when compared to the PD patients that remained dementia-free and to controls. Dementia-free PD patients were characterized by intermediate values of SS density values between healthy controls and PD with dementia. In this study, the authors also show EEG-slowing increase in PD that is enhanced in cases of dementia, thus supporting the hypothesis that a general slowing pattern in EEG might be considered as a biomarker for PD dementia, perhaps as a consequence of cholinergic denervation. Sleep spindles are involved in cognitive processing, including memory consolidation [29]; however, currently there are limited studies linking SS, RBD, and alpha-synucleinopathies with cognitive impairment.

Alterations in EOG signals during sleep have been observed. In particular, Christensen et al. used the energy calculated from wavelet decomposition in different frequency bands to differentiate controls and RBD/PD patients achieving sensitivity of 95%, specificity of 70%, and accuracy of 86.7% [30]. In a later study, EOG signals were used in an unsupervised data-driven approach to evaluate eye movements during sleep [31]. It was observed that PD and RBD patients reflect abnormal form and/or timely distribution of eye movements during sleep and that these abnormalities can be used to classify healthy controls versus PD/RBD with sensitivity of 95%, specificity of 80%, and accuracy of 90%. These studies confirm abnormalities in ocular movements that were observed in PD with video-oculography [32].

Alpha-synucleinopathies are characterized not only by micro-sleep abnormalities but also by macro-sleep changes. In a study performed by Arnaldi et al. [33], the authors showed the loss of physiological nocturnal increase in REM sleep duration and the loss of the increase of REM frequency across the night in RBD and PD with RBD patients. These changes suggest alterations in the circadian system in RBD pathophysiology. Generally, studies evaluating alterations in sleep macrostructure encounter difficulties due to the high inter-scorer variability in PSG evaluation [34]

and to the fact that there are several confounding factors in RBD evaluation, such as age [35], periodic leg movements [36, 37], sleep apneas [38], and night-to-night variability [39]. To overcome these problems related to subjective interpretation of PSGs, a data-driven approach based on EEG and EOG signals for sleep staging [40] has been applied to healthy controls, RBD and PD patients in order to identify abnormal patterns in macro-sleep structure. The data-driven method finds "topics" in EOG and EEG signals that correspond to different sleep stages, and for each epoch, the probability of each topic is calculated. In a first study, it has been observed that the altered amount of REM sleep and N3 and the altered ability of maintaining NREM and REM sleep characterize RBD and PD patients; thus, they might be considered biomarkers for PD development [41]. In a later study, wake, REM, NREM stabilities, and REM/NREM transitions were shown to be altered in RBD and PD. These patterns were evident only by applying validated data-driven automatic methods for sleep staging and not when the manual scoring was considered [42]. Figure 20.1 shows the topics for EEG channels, where each color represents the probability of a certain topic stage (i.e., sleep stage). It is possible to notice the increased fragmentation and lower stability in RBD and PD patients compared to the healthy control subject. These macro-sleep abnormalities might be the consequence of the involvement of brain stem areas in the early stages of synucleinopathies [43].

20.3 Evoked Potentials in RBD

The study of evoked potentials (EP) is a useful tool to evaluate the state of the nervous system and therefore offers insights in understanding abnormalities related to sleep diseases [44].

Many patients with PD suffer from pain and have impaired somatosensory function. Hypothetically, pain perception and somatosensory function could be altered already in a preclinical stage of PD. A study has investigated that, and the results showed that RBD and PD patients have abnormal response to pain stimulation using laser stimulation, suggesting that somatosensory impairment might be an early feature in the neurodegenerative process of PD [45]. In another study, de Natale et al. [46] observed higher rate of abnormal vestibular evoked myogenic potentials in RBD patients when compared to controls. Moreover, visual hallucinations are commonly observed in PD. Changes in visual EP have been associated with disease progression of PD and may potentially be modified by dopaminergic treatment suggesting involvement of retinal dopaminergic system and the REM sleep regulatory system [47]. Some studies have also shown altered visual EP and brain stem auditory EP, suggesting that brain stem visual and auditory passageways may be impaired in PD [48, 49]. These observations should be extended also to RBD patients.

A technique that is often used to analyze dysfunction in the brain stem is the electric blink reflex (BR). Alterations of BR have been observed in DLB but not in RBD or parkinsonism [50]. In another study by Peter et al. [51], a case of RBD patient with excessive startle response to visual stimuli was observed, which was probably caused by a pontine lesion and subsequent involvement of the bulbopontine reticular formation.

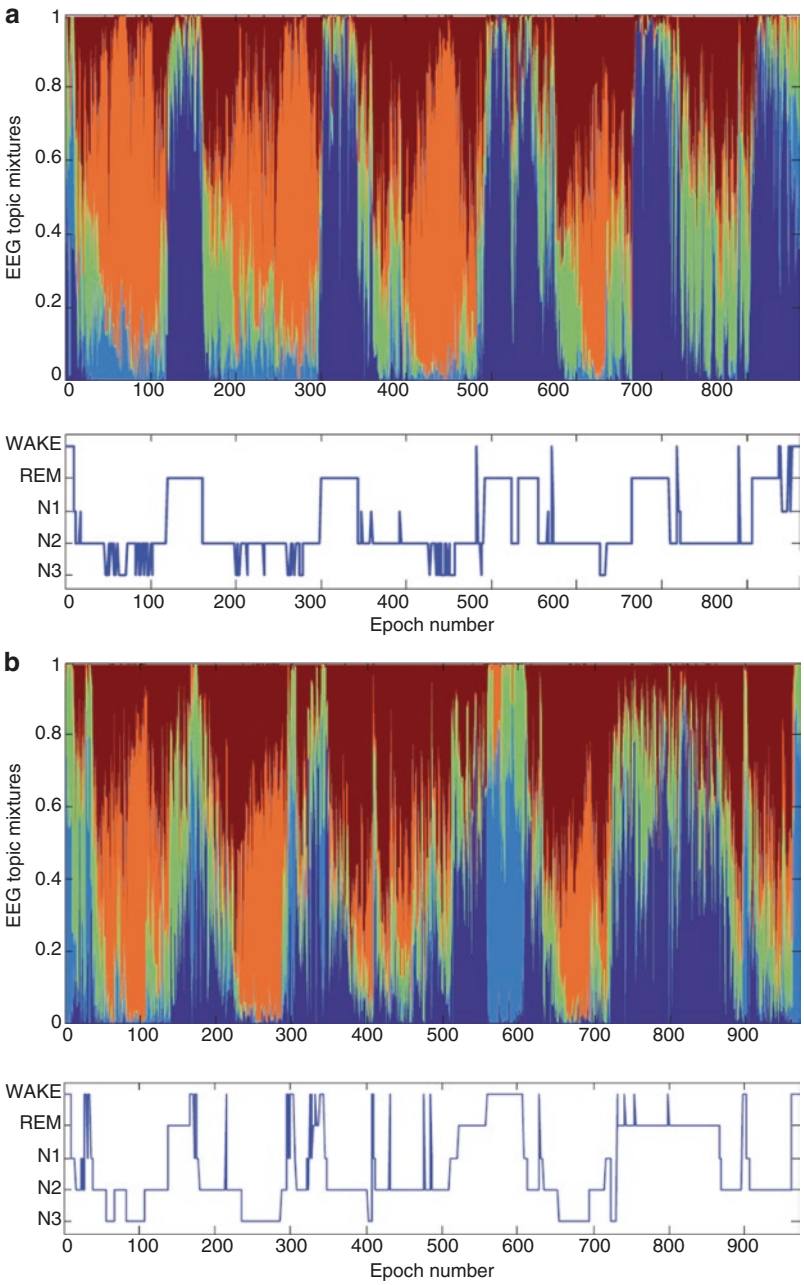

Fig. 20.1 Examples of EEG topic diagrams from a healthy control subject (**a**), an RBD patient (**b**), and a PD (**c**) patient. The figures are stacked percentage column charts, where a sleep epoch is presented as a vertical line possessing a mixture of colors. Each color presents an EEG (dark blue, light blue, green, orange, or red) topic, where the amount of color in each vertical bin presents the probability of the specific topic. The colors are comparable between diagrams. The manually scored hypnograms are provided below the topic diagrams [41]

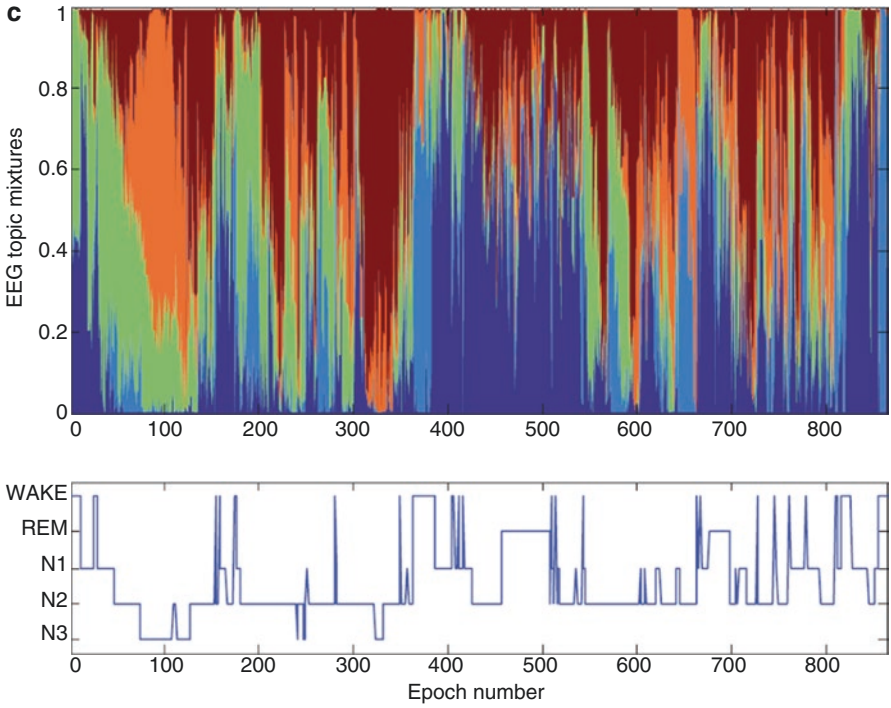

Fig. 20.1 (continued)

20.4 Other Electrophysiological Changes in RBD

Recently, also automated analysis of speech has shown interesting results in RBD/PD identification [52]. In particular, respiration, phonation, articulation, and timing showed abnormalities in RBD and PD patients, suggesting these features as a biomarker for PD development.

Analysis of other electrophysiological signals might offer new insights on RBD, and the integration of mathematical models and machine learning methods will be helpful for future RBD diagnosis and deeper scientific insights.

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Video Analysis of Behaviors and Movements in RBD

21

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21.1 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dream enactment allowed by a loss of physiological muscle atonia during REM sleep [1]. RBD usually manifests itself as the enactment of an unpleasant, action-filled, and violent dream to which the individual is being confronted, attacked, or chased by unfamiliar people or animals, leading frequently to sleep-related injury [2–5]. However, non-violent behaviors are also observed [6]. The behaviors during RBD include talking, laughing, shouting, screaming, swearing profanities, gesturing, reaching, grabbing, arm flailing, slapping, punching, kicking, sitting up, jumping out of bed, crawling, and running [1, 4, 6–10]. The behaviors are various, nonstereotyped, and complex. Walking is not common during RBD, and leaving the room is rare. However, among 203 consecutive idiopathic RBD patients, Frenandez-Arcos et al. reported that 24% of them left their bed occasionally, with some leaving the room and even the house. Although these behaviors were only displayed once or twice within several years of RBD history, these results indicate that ambulation during sleep does not exclude the diagnosis of idiopathic RBD [11]. The eyes usually remain closed during an RBD episode, with the person attending to the dream action and not to the actual environment [12, 13]. Typically, at the end of an episode, the individual awakens quickly; becomes rapidly alert; and reports a dream with a coherent story, with the dream action corresponding to the observed sleep behaviors [14]. Associated with these complex behaviors, patients also present elementary movements. Less impressive, they are more frequent and mostly the only movements observed on video recordings during REM sleep [15, 16].

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The diagnosis of RBD requires the presence of REM sleep without atonia (over a mostly accepted threshold of 18.2% of total REM sleep time when looking at the mentalis muscle alone [17]), associated with at least a history of abnormal sleep behaviors and/or abnormal behaviors during REM sleep recorded during video-polysomnographic (vPSG) monitoring [18]. According to a recent meta-analysis, based on a total of 28 studies with 6869 Parkinson's disease (PD) cases, nearly half of the patients suffered from RBD [19]. Older age and longer duration of the disease were risk factors for RBD in PD, while male gender was not a risk factor [19]. For patients, not reaching a sufficient level of REM sleep without atonia for diagnosing RBD, but presenting movements and/or vocalizations with a seemingly expressive, purposeful component detected on vPSG during REM sleep, Sixel-Döring et al. [20] have elaborated the concept of REM behavioral events (RBE). These RBE were associated with dream contents [21] and were found in 51% of all patients with de novo PD, while the complete ICSD-2 [18] criteria for the diagnosis of RBD were observed in only 25%. Thus, RBE was considered to be a potential marker for premotor manifestations of PD as a precursor to RBD.

In other synucleinopathies, the prevalence of RBD is even higher, reaching 86% in patients with dementia with Lewy bodies [22] and 90% in patients with multiple system atrophy (MSA) [23, 24].

Surprisingly, patients with PD have an improvement of their motor control during REM sleep with a disappearance of parkinsonism [25]. This improvement is also observed in patients with MSA, a L-dopa nonresponsive parkinsonian syndrome [26].

Patients with idiopathic RBD and RBD with PD also have frequently increased periodic limb movements of sleep (PLMs) on sleep recordings [27]. This increased frequency of PLMs, however, is not observed in other diseases such as MSA [28], where RBD is highly prevalent but PLMs are not, suggesting that these two phenomena involve different pathways.

21.2 Characteristics of the Movements During RBD

On video analysis, motor events in patients with severe clinical RBD and parkinsonism are frequent, reaching more than five movements per minute of REM [15]. These movements have a strong intraindividual variability in their type and frequency from a night to another [15]. Most events are elementary (83%), whereas complex behaviors are less frequent (13.5%). Even if there are many movements during RBD, these movements are very brief, so that only 9.2% (0.1–20%) of REM sleep time is associated with a motor activity [12]. The exploration of movements during RBD, recording the EMG of 13 different muscles, has shown that movements are more often distal than proximal [29]. On video recordings of patients with PD-RBD, movements involve six times more often the upper limbs and the face than the lower limbs [25]. Moreover, in patients with PD, where the disease is mostly asymmetrical, impairing more severely one side of the body than the other, movements during RBD are more often located in the more disabled side than on the less disabled side [25].

Comparing video-monitored movements during RBD episodes in patients with PD ($n = 29$) and in patients without parkinsonism ($n = 36$: idiopathic RBD, $n = 31$; narcolepsy, $n = 5$) to movements during wakefulness, RBD movements are different. They are faster and more often repeated, jerky, and apparently in connection with the dreams contents or, not self-centered, never associated with tremor, and rarely involve the environment in an appropriate manner. The jerky movements could be a result of the absence of a real target and the lack of somatosensory feedback, preventing an accurate adjustment of movements or linked to the absence of a smoothing effect [30]. During grasping movements, 48% of the patients have a specific posture of the hand (limp wrist with flexed digits), delineating a common motor signature of RBD [30]. The limp hands of patients with RBD share similarity with the flaccid hands of awake babies. Some RBD behaviors could thus result from activation of immature motor circuits. Eventually, the limp hand could result from simultaneous tonic digits and atonic wrist posture, secondary to an incomplete restoration of muscle tone.

21.3 Cortical Involvement in Movement Generation in RBD

The role of the cortex in the generation of movements of enacted dreams during RBD is increasingly confirmed. The behaviors that the co-sleepers report and that we observe on video recordings are elaborate, complex, nonstereotyped, and sometimes learnt. Behaviors such as making a political speech, giving an English lecture, singing a song, or smoking a cigarette that we collected suggest they result from the same cortical mechanisms as awake complex activities, rather than from primary automatisms [6, 25]. Moreover, the high proportion of face and arm movements during REM sleep that we noticed could be further evidence for a cortical involvement [25]. In fact these body parts are the most largely represented on cortical area. This is not in agreement with the theory that RBD could be archaic movements, determined by central pattern generators in the brainstem, subserving innate motor behaviors necessary for survival [31]. Nevertheless, a recent reconsideration on the source of the various pathological movements and behaviors in RBD merits attention, in regard to the brainstem as a source of some of the pathological twitches, movements, and behaviors, and in regard to sensory feedback from moving limbs in REM sleep being an important influence on the content of dream-enacting mentation in RBD [32].

This cortical involvement, clinically suspected, has been confirmed by neuroimaging studies. The involvement of the supplementary motor area (SMA) has been suggested by a first study showing that during an RBD episode in a patient with MSA there was an increased perfusion measured by ictal single photon emission computed tomography (ictal SPECT) in the SMA compared to two controls during REM sleep [33, 34]. The involvement of the SMA in the generation of movement has been confirmed in a larger study that showed by ictal SPECT an increased perfusion in the SMA during RBD in one patient with idiopathic RBD, one patient with PD and RBD, and two patients with narcolepsy and RBD [35]. The tracer was injected after at least 10 s of consecutive REM sleep and 10 s of disinhibited muscle tone accompanied by movements.

SMA is involved in the selection, the preparation, and the sequencing of movements [36] during wakefulness, but also dreamed movements during vivid dreams [37]. Interestingly SMA is hypoactive in patients with PD but seems to be overactivated during the movements of RBD [38].

21.4 Increased PLMs in Patients with RBD

The association between RBD and PLMs has been reported in idiopathic RBD [39], and the association between PLMs and PD is also well known [20, 28]. There is a significantly greater amount of PLMs in patients with PD and RBD compared to patients with PD without RBD [27]. Interestingly, Schenck et al. [40] have also noticed that the PLMs index in idiopathic RBD patients who eventually develop parkinsonism is higher than in patients who remain idiopathic after 6 years. Increased PLM index could be, in patients with idiopathic RBD, a further harbinger of future PD [41]. Moreover, it suggests that motor dysfunction in PD is not limited to REM sleep but also involves non-REM sleep and that both RBD and PLMs should be considered as parts of motor manifestations of PD [41]. Even if PLMs and RBD might have some anatomic link in PD [42], they must involve different pathways since, for example, RBD is very frequent in MSA [23], but PLMs indexes in MSA are not higher than in controls [28].

21.5 Comparison Between Movements While Awake and During RBD

Surprisingly, patients with PD are able, during their RBD, to do things that they are unable to do during wakefulness (Table 21.1). While awake, due to their parkinsonism, their movements are slow and have reduced amplitude, and their voice is muffled, whereas during RBD, they shout; have violent, strong, and fast movements; and have expressive faces. In order to explore this discrepancy, we conducted a prospective study exploring the quality of movement, facial expression, and voice during RBD in 100 consecutive patients with PD [25]. Fifty-nine percent of the patients had clinical RBD. All the co-sleepers (53/59) who were able to evaluate these three items during sleep reported that the patients had an improvement of at least one of them. By history, movements were improved in 87% of patients, speech was better in 77%, and facial expression was normalized in 47%. Thirty-eight percent of the bed partners reported that movements were “much better,” even in the most disabled patients. The video-monitored purposeful movements in REM sleep in patients off levodopa for 12–20 h were also surprisingly fast, ample, coordinated, and symmetrical, without obvious signs of parkinsonism, thus confirming the clinical impression of the co-sleepers. Surprisingly, while all patients had asymmetrical parkinsonism when awake, most of the time they used the more disabled arm, hand, and leg during the RBD.

Table 21.1 Examples of the discrepancy between movements during RBD and while awake in PD patients

Example of behavior during RBD	Dream content	Difficulties while awake
Singing loud "le temps des cerises," an old French song	I am dreaming I am under my shower, singing	Hypophonia, unable to sing
Going suddenly to the window, giving a head-butt to the window, breaking it	I am dreaming I am in a hotel room, an aggressor comes in. I want to protect myself, and I head-butt the aggressor	Difficulties walking alone
Sitting on his bed, doing large, fast movements with his hands and arms	I am dreaming that I am at work bottling water for "Perrier," transferring the bottles from a shelf to another	Difficulties with doing large movements, bradykinesia
Squatting on the bed, waving his arms as if flying, shouting "pin pon" (the two-tone sound of a siren) with a duck voice	I am a police duck, flying after a pigeon thief	Unable to squat, bradykinesia, hypophonia
Crying, with a very strong emotion of sadness on her face	No memory of this dream	Strong amimia

Another study, exploring laughing during RBD, also found a strong dissociation between hypomimia and hypophonia during the daytime and pronounced facial expressions and loud laughing during sleep on video recordings [10]. The restored motor control during RBD observed in these studies could suggest a transient "levodopa-like" reestablishment of the basal ganglia loop during REM sleep. However, our other study [26], demonstrating the same improvement of motor control during RBD in patients with MSA, a poorly responsive to levodopa parkinsonian syndrome, does not sustain this hypothesis. We however observed a peculiar aspect of movements during RBD that even if they were not parkinsonian, they were also not normal, being jerky, rough, and not smooth. This aspect was not during a succession of several sequences of movement, i.e., the flow from one sequence to another, but rather it was a fragmented aspect inside the same movement. This abnormal aspect suggests that movements during RBD may use other functional pathways while bypassing the pathological basal ganglia. That this pattern was also observed in patients without any movement disorder [30] (idiopathic RBD and RBD in narcolepsy) strengthens the hypothesis of a bypass of the basal ganglia system during RBD as a basic feature of RBD.

The bypass of the basal ganglia during RBD has also been confirmed by neuroimaging. First the ictal SPECT study described before in four patients with RBD has not only shown the increased activity of the SMA but also the absence of activation of the basal ganglia [35]. In healthy subjects, voluntary leg movements during wake, as measured by blood oxygen level-dependent functional MRI, result in activations in the primary sensorimotor cortex, the supplementary motor area, cingulate motor area, the anterior cerebellar vermis, both cerebellar hemispheres, thalamus, and right putamen [43]. In this study, where movement during RBD also involved the legs, there was sparing of the activation of the basal ganglia.

An electrophysiological study has also confirmed this bypass, showing evidence for alternative motor networks in RBD, recording local field potentials in the subthalamic nucleus (STN) and scalp EEG during sleep in humans with PD and RBD. The STN has been identified as a key structure for movement control, and many studies have linked hypersynchronous neuronal activity in the low β band (12–20 Hz) of STN neurons with motor impairment [44, 45]. Within this framework, STN deep brain stimulation is thought to counteract the pathologically elevated activity, leading to significant motor improvement [46]. In this study, time-locked, event-related β band oscillations were calculated during movements in REM sleep compared with movementsREM sleep behavior disorder (RBD): in the waking state and during NREM sleep. Spectral analysis of STN local field potentials revealed elevated β power during REM sleep compared with NREM sleep, and β power in REM sleep reached levels similar to in the waking state. Event-related analysis showed time-locked β desynchronization during awake movements. In contrast, this study showed significantly elevated β activity before and during movements in REM sleep and NREM sleep. Cortico-subthalamic coherence was reduced during REM and NREM movements, suggesting that sleep-related movements were not processed by the same corticobasal ganglia network as movements in the waking state. The authors concluded that the seemingly normal motor performance during RBD in PD patients might be generated by activating alternative motor networks for movement initiation. These findings support the hypothesis that pathological movement-inhibiting basal ganglia networks in PD patients are bypassed during sleep.

Similar questions to those just discussed regarding RBD associated with PD and MSA as synucleinopathy neurodegenerative disorders were raised regarding pre-clinical RBD associated with a tauopathy neurodegenerative disorder in a case report entitled, “A first case of progressive supranuclear palsy and pre-clinical REM sleep behavior disorder presenting as inhibition of speech during wakefulness and somniloquy with phasic muscle twitching during REM sleep” [47]. In this case, there was pathologically linked, state-dependent speech motor inactivation in wakefulness and excessive speech motor activation in REM sleep.

The posterior part of the SMA, also called SMA proper, sends direct corticospinal efferents [48] and is more closely related to movement execution [49]. This specific part of the SMA could be the commander of the generation of movement during RBD, bypassing the basal ganglia.

21.6 REM Sleep Motor Events in Idiopathic RBD and PD-RBD

Video-polysomnography was used to characterize motor events (ME) in 14 PD-RBD and 18 idiopathic (iRBD) RBD cases [50]. ME were nonemotional, occurred mainly in the upper limbs, and were mostly simple, distal, and focal. ME were mostly non-violent. There were no significant differences in ME features between PD-RBD and iRBD groups. Therefore, the presence of wakeful motor dysfunction in PD patients with RBD did not affect ME features, and the ME activity during REM sleep in RBD-PD patients resembled that of iRBD patients.

Conclusion

The precise exploration of movement during RBD has led to the development of hypotheses concerning the generation and the execution of movement during the particular state of REM sleep. These hypotheses have been sustained by recent neuroimaging studies. They strongly suggest that in RBD, the SMA is involved in the generation of movement and that during the execution of movement, the basal ganglia are bypassed.

Note Added in Proof: A recent publication pertaining to RBD behavioral analysis, and another publication on alternative motor networks in RBD merit inclusion: (1) Nguyen-Michel VH, Solano O, Leu-Semenescu S, et al. Rapid eye movement sleep behavior disorder or epileptic seizure during sleep? A video analysis of motor events. Seizure 2018; doi: 10.1016/j.seizure.2018.03.021. [Epub ahead of print] (2) Hackius M, Werth E, Suruucu O, Baumann CR, Imbach LL. Electrophysiological evidence for alternative motor networks in REM sleep behavior disorder. J Neurosci 2016; 36 (46): 11795-11800.

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Clinical Vignettes: Illustrative, Unusual, and Challenging RBD Cases

22

Alon Y. Avidan

22.1 Case A

A 62-year-old right-handed man with a recent diagnosis of voltage-gated potassium channel antibody-associated limbic encephalitis (VGKC-LE) presented to the resident continuity clinic with rapid onset memory decline and "nightmares" at night temporally associated in time with the onset of the above diagnosis. His wife reported that he had been having episodes of acting very aggressively toward her at night. The patient himself recalls vivid dreams consisting of intruders attempting to gain entry to their house. These dream enactment behaviors consist of arm stiffening, attempts to grab at objects, and vocalization, to more dramatic episodes where he is witnessed to be punching and kicking his wife during sleep, necessitating her to sleep in the guest bedroom out of fear that she would get seriously injured during these episodes. His past medical history consists of dyslipidemia and hypertension and his medications include simvastatin and hydrochlorothiazide. Neurological examination revealed significant short-term memory loss and frontal release signs including positive palmomental and snout reflexes. The rest of the examination was otherwise normal.

His brain MRI depicted bilateral mesial temporal hyperintensities on fluid-attenuated inversion recovery and T2-weighted sequences as illustrated in Fig. 22.1a. Given the concerns for dream enactment behaviors, he was referred and underwent video-polysomnography (vPSG) which depicted leg kicking, body movement, and talking with corresponding augmentation of limb EMG tone during REM sleep (Fig. 22.1b), which confirmed the diagnosis of REM sleep behavior disorder.

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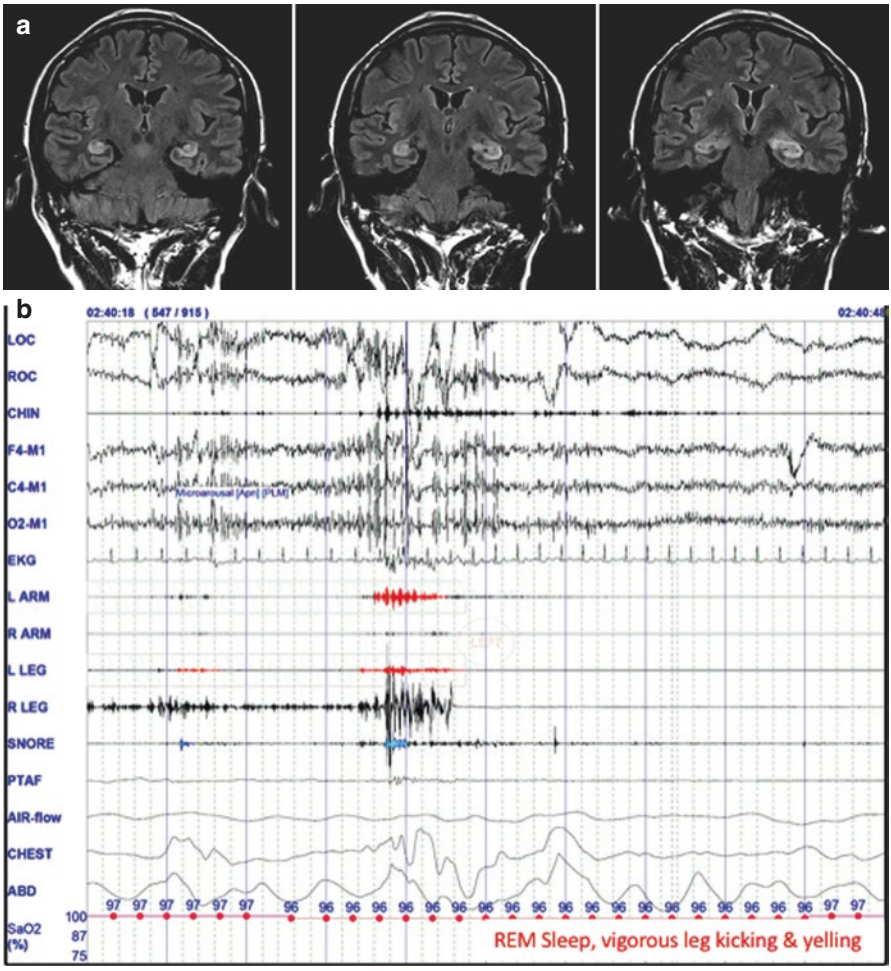

Fig. 22.1 (**a**) Coronal fluid inverse recovery (Flair) brain magnetic resonance imaging showing mesial temporal hyperintensities with sparing of midbrain. (**b**) Polysomnogram demonstrating electromyogramic (EMG) augmentation during REM sleep associated with dream enactment behavior. Illustrated here is a 30-second epoch of REM sleep without atonia, manifested by increased muscle activity during REM sleep, mainly involving the right leg (LEG) EMG associated with increased motor activity where the patient was kicking his legs as documented by annotations provided by the sleep technologist. *The International Classification of Sleep Disorders* 3rd Edition Diagnostic Criteria for RBD includes the following: (1) PSG abnormality—elevated EMG tone during REM sleep in either submental or limb leads. (2) Either a history of dream enactment behavior or observation of abnormal REM sleep behavior during the vPSG. (3) Absence of EEG epileptiform activity during REM sleep. (4) The disturbance is not explained by another sleep/medical/neurological/mental disorder and is not related to medication/substance use. Channels are as follows: LOC and ROC = electrooculogram, left and right outer canthus, CHIN (chin electromyogram), electroencephalogram (right frontal, central, and occipital referred to left mastoid—F4-M1, C4-M1, O2-M1), electrocardiogram (EKG) channel, right and left limb EMG (R and L leg and arm), snore channel (SNOR), PTAF, airflow channel, respiratory effort (chest and abd), and oxygen saturation (SaO2) (Copyright to Alon Y. Avidan, MD, MPH)

The morning questionnaire indicated that he had a dream where he was incarcerated and was trying to get away.

The patient was treated initially with intravenous immunoglobulin (IVIG) as an inpatient and then monthly plasmapheresis for the next 2 months. As clinical improvement was not apparent, immunosuppressive therapy with corticosteroids was added, after which his memory and cognitive symptoms improved dramatically. Dream enactment behaviors resolved completely about 6 weeks following introduction of immunosuppressive therapy.

22.1.1 Discussion: Case A

Voltage-gated potassium channel antibody-associated limbic encephalitis (VGKC-LE) is an acquired autoimmune encephalitis that causes neuropsychiatric problems including memory impairment, behavioral changes, hyponatremia, and seizures. More recently VGKC-LE has been linked with RBD, which is illustrated here. One study by Iranzo et al. examined six consecutive patients with VGKC-LE and found five out of six patients had definite RBD confirmed with vPSG that showed REM sleep without atonia [1]. Lopez et al. performed a retrospective analysis of hospital data showing RBD symptoms in 13 out of 13 patients identified with VGKC-LE over a 10-year period [2]. Lin et al. reported on a single case of RBD developing in a patient with acute aseptic limbic encephalitis lending further support to the implication of limbic system impairment in the pathogenesis of RBD [3] (Chap. 8 contains an extensive discussion of RBD associated with autoimmune disorders).

22.2 Case B

A 79-year-old Hispanic man presented with a 2-year history of dream enactment behaviors. He denied experiencing any difficulties with anosmia, constipation, morning orthostatic symptoms, or loss of color vision. His most dramatic dream enactment led to a fracture of his big toe as he was dreaming of playing soccer and ended up kicking his foot against the wall, sustaining the injury. The patient underwent a vPSG which confirmed the presence of REM sleep behavior disorder. He was invited to return to the sleep disorders clinic to review the new diagnosis and how it explained his violent dream enactment.

During the follow-up visit, he was placed on melatonin, 5 mg TR (time release) at bedtime, as the episodes occurred 2–4 times per week and have resulted in injury. Management with melatonin provided excellent amelioration of the patient's symptoms, and he only has occasional monthly spells in which he may speak or yell out but at a volume that does not awaken him or his wife. His primary care physician then sent the patient back for a sleep consultation to review the prognosis of RBD, as the physician has read that this RBD may place the patient at risk for a neurodegenerative condition.

At this visit, the sleep medicine fellow provides a disclosure about the prognostic implications of the condition to the patient and his wife who joins him. The patient

is provided prognostic data that about 70% of patients with RBD may go on to develop a neurodegenerative disorder. While his wife is reassured that this is an important data for them to be aware of, it draws immediate negative feedback from the patient who claims that he would have rather not have been told about these statistics, especially since he cannot control "his destiny and he would have rather not known about something that he cannot control."

22.2.1 Discussion: Case B

RBD has been noted to be highly associated with the future development of various alpha-synucleinopathies, particularly Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multisystem atrophy (MSA) [4–6]. In a published cohort of 174 idiopathic RBD (iRBD) patients followed longitudinally, the risk of a defined neurodegenerative syndrome from the time of iRBD diagnosis was 33.1% at 5 years, 75.7% at 10 years, and 90.9% at 14 years; and the median conversion time was 7.5 years [7]. (The topic of iRBD and its longitudinal course is covered in Chap. 4.)

The case illustrates the potential feedback when patients would have rather not been told that they could present with a neurodegenerative disorder in the setting of RBD. While in the author's experience, most patients would welcome a discussion of prognostic implications of a disorder, few would view this discussion as undesirable or threatening. It has been proposed that the "watchful waiting" approach to disclosure may spare patient's periods of undue anxiety associated with knowing that they may be eventually diagnosed with a neurological condition, but prevents patients from actively preparing future life decisions or could potentially prevent them from seeking medical attention when novel treatments do become available to delay or prevent the development of alpha-synucleinopathies. Also, patients themselves, or their families and friends, would most likely discover the RBD-parkinsonism link on the Internet, which is another compelling reason for "up front" prognostic disclosure at the time of RBD diagnosis.

Full disclosure, as in this case, has the advantage in providing patients and loved ones prognostic data to help with future life planning and allowing providers the opportunity to counsel patients about safety education and injury prevention techniques, and future trials focused on neuroprotection. On the downside, full disclosure may be viewed as an unsolicited discussion of a non-actionable condition which could infringe on patient autonomy and lead to unnecessary anxiety [8].

Given that a patient diagnosed with RBD has at least a 2/3 risk of developing an alpha-synucleinopathy, this discussion is unavoidable. While it is impossible to predict whether a patient will develop an alpha-synucleinopathy neurodegenerative condition, the timeline for emergence, and which specific subtype, the health provider treating the patient must consider (1) the difference between disclosing a diagnosis of RBD and disclosing the neurological risk from the diagnosis of RBD of RBD, (2) whether to disclose this risk to patients, and (3) if deciding to disclose the risk, the appropriate timing of such a conversation [9]. Further, the clinician should assess the patient's educational level and cultural and ethnic background to ensure that the discussion will be well understood, and recalibrate the discussion to fit it with the

Table 22.1 Possible approaches to disclose a diagnosis of REM sleep behavior disorder[a]

The argument for "watchful waiting" approach	
Favoring watchful waiting	*Against watchful waiting*
Prevents exposing patients to a needless level of anxiety associated with a possibly imminent neurodegenerative condition, which they cannot prevent nor control	Prevents patients from making proactive future life decisions, such as taking a long-awaited (family) vacation and financial and retirement planning
	By not knowing that they may be at risk for neurodegenerative disorders, patients may lack awareness of potential drug trials or novel therapeutics that could delay or prevent the development of synucleinopathies
The argument for a "full disclosure" approach	
Favoring full disclosure	*Against full disclosure*
Allows patients and family members to actively conduct future life planning in the context of potentially imminent neurodegeneration	Although disclosure is clinically necessary about the diagnosis of RBD and its increased risk for injuries, and therefore the need for risk modification and safety interventions, disclosure of the neurodegenerative risk associated with the diagnosis of RBD is not appropriate as it provides an unsolicited disclosure about a diagnosis of a non-actionable condition

Patients with REM sleep behavior disorder (RBD) may be counseled about prognostic implications concerning future phenoconversion to neurodegeneration. The table provides some of the arguments for "watchful waiting" vs. "full disclosure" for the clinician to consider at the time of seeing the patient in clinic after the vPSG diagnostic confirmation of RBD
Modified from [8]

[a]The reader is advised that no one approach is preferred as patient presentation is unique and expectations can vary considerably. Prognostic counseling for patients ≥50 years old, where phenoconversion data are more robust and definitively demonstrated, may need to be recalibrated when counseling younger patients (<50 years old), where RBD as yet has an indeterminate correlation to future neurodegeneration, especially in younger patients with prescribed antidepressant medications

patient's educational level, sophistication, and comprehension. A summary of the pros and cons concerning watchful waiting vs. full disclosur*e* of RBD, when providing prognostic counseling, is provided in Table 22.1. Also, a recent report addressed the issue of iRBD frequently being prodromal Parkinson's disease and related neurodegenerative disorders and recommended that the identification of RBD should prompt "the early involvement of rehabilitation and/or development of home exercise plans [that] may aid in prolonging and even increasing function, independence, and quality of life should such neurodegenerative disorders develop later in life" [10].

22.3 Case C

A 53-year-old man presented to the neurology inpatient service with severe hypersomnolence, dream enactment behavior, bona fide cataplexy, and altered consciousness in the setting of biopsy-proven neurosarcoidosis of the hypothalamus. Neuroimaging demonstrated hypothalamic destruction due to sarcoidosis. CSF assay for hypocretin demonstrated complete absence of the peptide with a level of 0 pg/mL.

Narcolepsy type 1 (NT1) represents dysfunction of the hypocretin (orexin) system which stabilizes sleep and wakefulness. The majority of patients have NT1 low or undetectable levels of hypocretin-1 in the cerebrospinal fluid (CSF). Pathologically low hypocretin levels have been documented in cases of "secondary narcolepsy," which are caused by direct insult to the hypocretin (orexin)-producing cells in the hypothalamus in the setting of CNS etiologies, including neurosarcoidosis [11–13]. Physical examination revealed a lethargic, thin man who awakened intermittently to verbal stimuli, but held a very short attention span of approximately 5–10 s, then lapsing back to sleep. Brain magnetic resonance imaging (MRI) indicated involvement of the hypothalamus (Fig. 22.2 [I, II, III]), with both T2 and T1 post-contrast hyperintensity within that region.

Polysomnography documented left leg kicking with corresponding augmentation of limb EMG tone during REM sleep (Fig. 22.3), which together with his DEB confirmed the diagnosis of REM sleep behavior disorder.

Unfortunately, management represented a significant challenge, as both bedtime melatonin and clonazepam worsened the patient's hypersomnia. Analeptics such as modafinil and armodafinil and stimulants worsened the patient's dream enactment spells. Sodium oxybate, which would have provided control of sleepiness, cataplexy, and RBD (based on recent reports) [14–16], would have been problematic as the patient developed the syndrome of inappropriate antidiuretic hormone secretion (SIADH), in the setting of panhypopituitarism, and was running hyponatremia. The use of 6–9 g of daily oral sodium load could have resulted in central pontine myelinolysis (CPM) with permanent neurologic deficits. The patient's quality of life was deteriorating as he was sleepy during the day and was combative at night, to the point of needing nightly restraints, bed padding, and meticulous attention to safety issues. The use of temazepam (15 mg), clonazepam (0.125 mg), melatonin (3 mg) at night, and armodafinil (150 mg) in the morning, coupled with light exposure in the morning hours and early afternoon, provided adequate control of both somnolence and dream enactment behaviors, while he continued to have 1–2 episodes of flailing of the arms per week, which did not result in sleep disruption (Chap. 9 discusses Lesional RBD, and Chap. 11 discusses RBD with narcolepsy).

22.3.1 Discussion: Case C

The patient's symptoms and studies represent a central nervous system hypersomnia in the form of NT1, as defined by the *International Classification of Sleep Disorders-3*, resulting from significant hypothalamic destruction due to neurosarcoidosis. NT1 is characterized by selective loss of hypocretin-producing neurons in the hypothalamus. Hypocretin (orexin) is a neuropeptide of hypothalamic origin that promotes wakefulness and stabilizes sleep and REM sleep-associated muscle atonia via the REM-on glutamatergic neurons [17] through projections to the medulla and spinal cord. These mutually inhibitory interactions of the REM-on and REM-off neurons form the previously conceptualized flip–flop switch [18] that enhances sleep-wake state transition and predisposes those with hypocretin (orexin) deficiency to experience pathologic conditions.

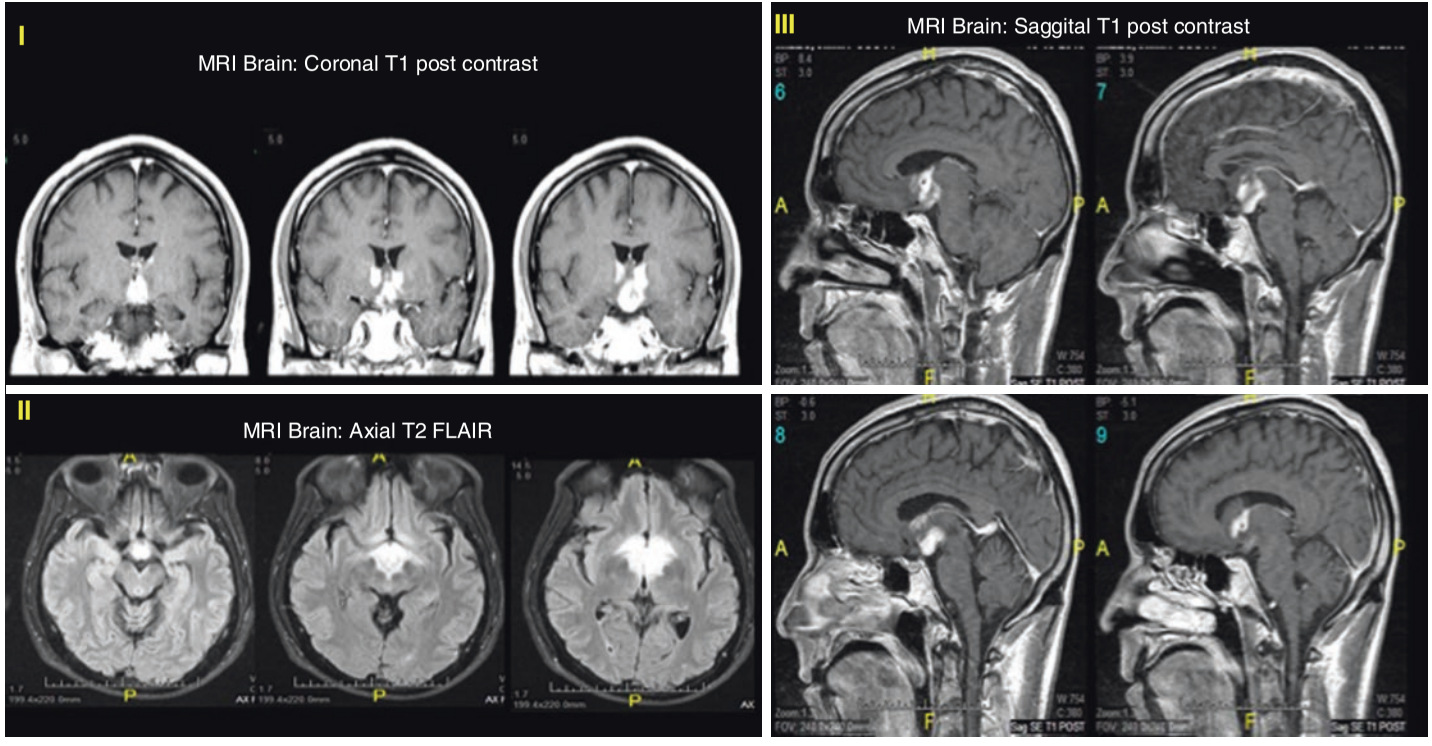

Fig. 22.2 (I) Coronal T1 post-contrast (II) axial T2 Flair and (III) sagittal T1 post-contrast MRI images of a patient with neurosarcoidosis who presented with hypersomnolence, cataplexy, and dream enactment behavior. The T1- and T2-weighted MRI images illustrate hyperintensities impacting the diencephalon. T2 images highlight hyperintensity in the anterior hypothalamus, consisting of abnormal signal lining the mildly expanded anterior third ventricle. No brainstem involvement appeared in MR images at that time, nor were there any detected lesions of the locus coeruleus or raphe nuclei

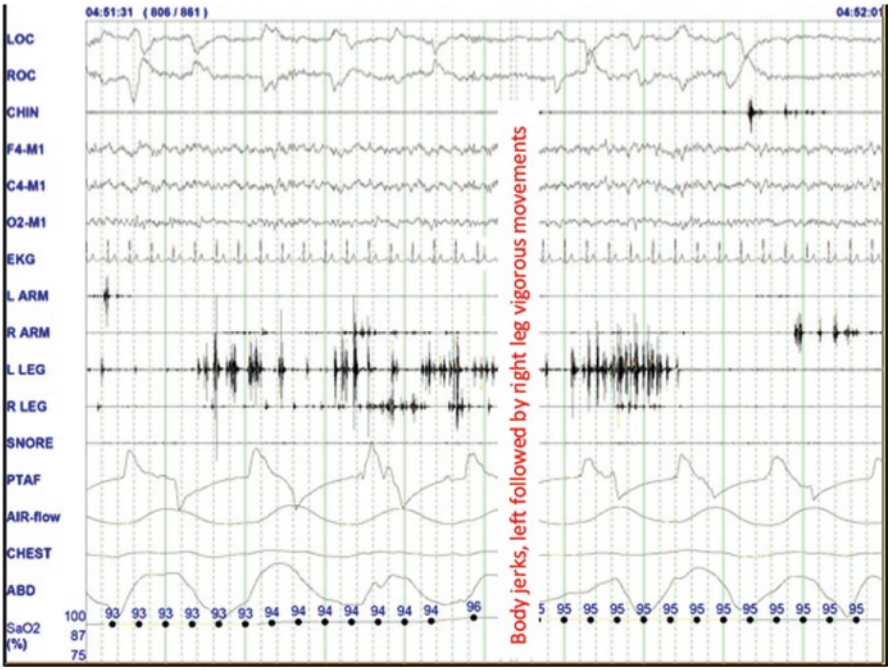

Fig. 22.3 Polysomnogram depicting dream enactment behavior in a patient with hypocretin deficiency syndrome in neurosarcoidosis of the hypothalamus. This 30-second epoch during REM sleep illustrates REM sleep without atonia, manifested by increased muscle activity during REM sleep, including body jerks, left leg followed by right leg vigorous movements. Channels are as follows: LOC and ROC = electrooculogram, left and right outer canthus, CHIN (chin electromyogram), electroencephalogram (right frontal, central, and occipital referred to left mastoid—F4-M1, C4-M1, O2-M1), electrocardiogram (EKG) channel, right and left limb EMG (R and L leg and arm), snore channel (SNOR), PTAF, airflow channel, respiratory effort (chest and abd), and oxygen saturation (SaO2) (Copyright to Alon Y. Avidan, MD, MPH)

Hypocretin deficiency in this case contributes to three pathologic sleep disturbances: (1) severe hypersomnolence and pathognomonic of narcolepsy, (2) Impaired hypocretin system may destabilize motor regulation during wakefulness and during sleep, resulting in cataplexy, and (3) REM sleep behavior disorder.

To help explain this physiologically, emerging data illustrate that hypocretin neurons project directly onto the motor neurons in the spinal cord and send excitatory projections to the single subset of REM-on neurons of the REM flip–flop switch. Hypocretin deficiency in the setting of secondary narcolepsy has been correlated with a more significant motor activation during REM and non-REM sleep [19]. Hypocretin may be responsible for stabilizing the REM-on and REM-off regions of the brain and could also play a key role in motor neuron inhibition, so diminished hypocretin levels would lead to unstable REM regulation of muscle atonia, conferring to a state of REM sleep without atonia [20]. It is conceivable that a state of hypocretin deficiency could confer a state of relative instability of

wake-sleep regulation and REM sleep motor dysregulation [20], which explains the state of severe sleepiness in this patient as well the coexistence of cataplexy and RBD.

22.4 Case D

A 65-year-old male presented with episodes of dream enactment spells at the frequency of 2–4 times per week. He had mostly good recollections for these events, but was mostly asymptomatic the next day. His wife, on the other, experienced significant insomnia as she was worried about sleeping next to him and more recently had begun to experience daytime sleepiness as she spent many hours awake in bed resulting in curtailment of total sleep time. The patient's spells were shortened and improved in response to his wife's voice telling him that "he was just having a bad dream and everything is OK."

He proceeded to undergo a diagnostic vPSG which confirmed the presence REM sleep without atonia, meeting the American Academy of Sleep Medicine Scoring Criteria for REM sleep behavior disorder. His apnea-hypopnea index was 0.5 and the minimum oxygen saturation was 93% without any snoring present. His periodic limb index was 0. The patient was started on melatonin at 5 mg TR, which according to his wife improved the episodes dramatically. Unfortunately, he was unable to tolerate the treatment due to severe sleepiness the next day. Lowering the dose of melatonin to 3 or 1 mg did not resolve the sleepiness. Switching to ramelteon, a melatonin receptor agonist, which has been shown to be efficacious in RBD [21], once again resolved DEB, but did not resolve daytime sleepiness. The patient was also sequentially placed on clonazepam, 0.125 mg; pramipexole, 0.125 mg; temazepam, 7.5 mg; low-dose diazepam; and low-dose lorazepam at bedtime, which controlled DEB, but also unfortunately induced sleepiness the next day.

Successful management of the patient's DEB spells was finally achieved with the use of the Posey Sitter Elite™ Alarm (Posey Products, LLC http://www.posey.com/sites/default/files/product-docs/M6223-Posey®-Sitter-Elite®-Alarm.pdf), which he purchased online at the advice of his sleep physician. He recorded his wife's voice using the Alarm's custom voice recording mode allowing the alarm to trigger when he experienced a dream enactment behavioral spell. This resulted in a dramatic reduction of his spell frequency without needing to take pharmacologic agents on a nightly basis with subsequent sedation. Figure 22.4A and B illustrates the Posey Alarm setup provided by the patient.

22.4.1 Discussion: Case D

The Posey Alarm has previously been reported by Howell et al. as an alternative treatment for patients with pharmacologically refractory RBD [22]. The customized bed alarm has the advantage of augmenting medical therapy in those with refractory RBD who experience injurious DEB, as in this patient. As in the patient just

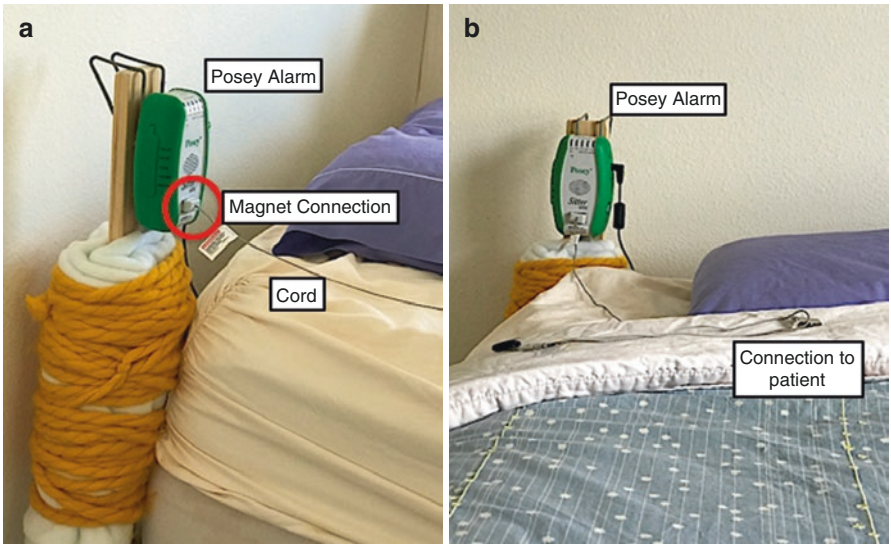

Fig. 22.4 Modified bed alarm (Posey Alarm setup) provided by patient in case D. Illustrated in Panel A is the Posey Sitter Elite™ Alarm (Posey Products, LLC) secured to a wooden post by the patient's mattress. The post itself was padded in such a manner so as to avoid potential injury should the patient move his limbs against it during his dream enactment behavioral spells. The red circle in Panel A illustrates the connection of the magnet to the Posey Alarm. The cord is connected to the patient (Panel B). When the patient experiences a dream enactment spell, the cord is polled, the magnet is disconnected, the circuit is broken, and the alarm is triggered, sounding the bed partner's voice, calmly relaxing the patient back to sleep

presented, who ultimately reported extinction of his bothersome and injurious violent dream enactment, Howell et al. speculate that the modified bed alarm attenuated violent DEB in RBD by decreasing anxiety during the night through the use of a calming, familiar voice (mostly the spouse).

One speculative mechanism of action may be related to the reduced auditory threshold during REM sleep, making patients likely to respond to the verbal stimulation by hearing the calming voice of their spouse [22]. The patient in case D continues to maintain a separate living quarter than his wife, but his sleep was not fragmented, but nor was his wife's. Ultimately, they were both able to enjoy a good quality sleep and subsequently good quality of life which was the most important therapeutic goal.

22.5 Case E

A 42-year-old woman with a history of depression is referred for evaluation of "nightmares" by her psychiatrist. She has never experienced any unusual events at night as a child and does not report any history of snoring or restless leg symptoms. Interestingly, the episodes began to be reported by her boyfriend as soon as she begun treatment with venlafaxine when her depression became refractory to

psychological intervention. He was repeatedly punched by her and noted that she would be yelling profanities at him, which was extremely out of character for her, even when she was emotionally upset. She reported these to her psychiatrist and was told that she must be under stress and was referred to cognitive and behavioral therapy (CBT). The patient denied feeling stressed, but complied with therapy as she did not want to disrespect the opinion of her psychiatrist.

A month after undergoing CBT, she returned to the psychiatrist indicating that her life "was a mess." Her boyfriend was afraid to sleep next to her as he was constantly being punched and kicked, and the CBT was not helping reduce the frequency or severity of the nocturnal spells. The episodes were occurring at around 3–4 AM and almost nightly. She has recollection of these spells and noted that they would occur following a dream sequence in which she would be confronted by intruders in her house, usually thieves, and felt imminent danger trying to escape from them or confront them.

The psychiatrist suspected that the patient experienced post-traumatic stress disorder (PTSD) and nightmares as she revealed that she was previously involved in a hostage situation as a bank teller 1 year earlier, and he placed the patient on prazosin at bedtime. He also asked a colleague to assist the patient with image rehearsal therapy (IRT) of nightmares. While both prazosin and IRH are effective treatments for nightmare disorder and PTSD [23, 24], the patient failed to respond. The psychiatrist eventually decided to send the patient for a sleep study with a primary concern of nightmare disorder.

The staff physician who triaged the referral suspected that the patient's diagnosis was more likely REM sleep behavior disorder, as opposed to nightmare disorder, and so the vPSG was modified to employ an expanded EMG montage and high-definition video monitoring. The patient underwent a vPSG study which captured one of her typical spells during REM sleep, as illustrated in Fig. 22.5. The episode featured yelling and vigorous body movement as the patient was trying to confront a supposed intruder, thus confirming the presence of REM sleep behavior disorder (Chap. 10 discusses RBD associated with antidepressant medications and psychiatric disorders).

22.5.1 Discussion: Case E

The case illustrates several points: (1) under-recognition of RBD in the face of psychiatric comorbidities; (2) delayed recognition of RBD secondary to the use of antidepressants, with prolonged use of the offending antidepressant instead of a rapid switch to a safer antidepressant; and (3) attribution of a potentially injurious parasomnia to nightmares or to "stress."

The link between antidepressants and RBD was initially made in 1992 when Schenck and colleagues reported on a group of adults treated with fluoxetine or tricyclic antidepressants, reporting that 2.64% developed RBD-like spells in response to pharmacotherapy [25]. A follow-up study in 2011 from the Washington University group by Ju et al. reported on changing demographics of RBD, depicting a more balanced gender distribution in patients under 50 years of age in whom

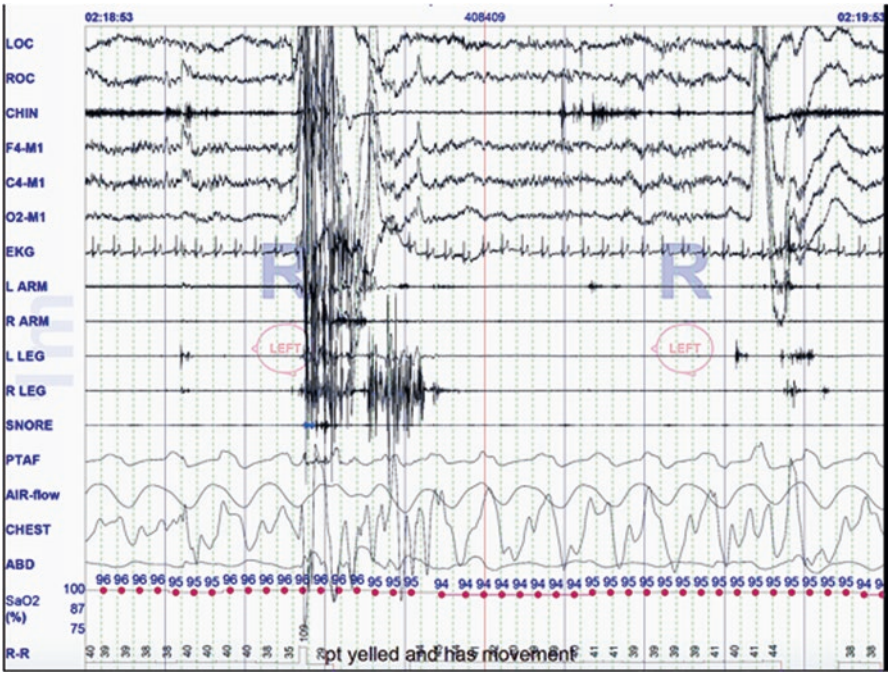

Fig. 22.5 Diagnostic polysomnogram illustrating a typical spell experienced by the patient presented in case E. This is a 60-second epoch during REM sleep depicting yelling, and vigorous augmentation of motor activity with REM sleep without atonia, manifested by increased electromyographic activity during REM sleep. Channels are as follows: LOC and ROC = electrooculogram, left and right outer canthus, CHIN (chin electromyogram), electroencephalogram (right frontal, central, and occipital referred to left mastoid—F4-M1, C4-M1, O2-M1), electrocardiogram (EKG) channel, right and left limb EMG (R and L leg and arm), snore channel (SNOR), PTAF, airflow channel, respiratory effort (chest and abd), and oxygen saturation (SaO2) (Copyright to Alon Y. Avidan, MD, MPH)

neurodegenerative disease was uncommon [26]. Interestingly, this cohort demonstrated a high rate of antidepressant use, as in the case just presented, suggesting a potentially causal role for antidepressants in RBD [26].

In an important study in 2013, Postuma et al. reported on their observation of 100 of patients with idiopathic RBD, 27 of whom reported using antidepressants, over an 8-year period. The authors specifically asked the question whether antidepressants-associated RBD conferred the same risk for alpha-synucleinopathy as one would observe for idiopathic (or more properly cryptogenic) RBD. What the authors demonstrated was quite intriguing: patients with RBD on antidepressants were more likely to exhibit significant markers of neurodegeneration compared to controls, and withdrawal of antidepressants did not reverse the loss of REM sleep atonia, implying that antidepressants uncover preexisting subclinical REM-related EMG muscle augmentation [27].

The patient presented with the typical features of RBD that were failed to be recognized by her treating psychiatrist, who attributed the RBD symptoms to PTSD, which can be comorbid in patients with RBD [28], and so it was not an unreasonable diagnostic presumption. Nevertheless, as Postuma et al. concluded in their study [27], dream enactment behavior in the setting of antidepressant exposure should be viewed as important possible or probable indicator of an evolving neurodegenerative process, after vPSG confirmation of the RBD diagnosis. These patients could become enrolled in future clinical trials of neuroprotection (once available), as discussed in Chap. 45.

Healthcare practitioners in general, and psychiatrists in particular, should be aware of the potential risk of antidepressants for inducing REM sleep without atonia (RSWA), and promoting RBD emergence, especially since antidepressants are among the most frequently prescribed medications. Physicians should counsel their patients not only to be aware of the commonly associated treatment-related side effects related to these agents but to also be aware of the potential for RSWA and potentially injurious dream enactment behaviors associated with these agents [29].

Conclusion

REM sleep behavior disorder represents an important neurologic condition which is likely to become more prevalent as the population ages. It's incumbent upon primary physicians to recognize its essential semiology and for specialists to recognize specific risk factors, not only alpha-synucleinopathies but also paraneoplastic syndromes, limbic encephalitis, hypocretin deficiency states, and exposure to antidepressants. In advising patients about the risk for neurodegeneration, it is important for the primary care physician to recognize the patient's educational and ethnic background and display sensitivity and transparency while respecting the patient's autonomy and right to full disclosure about their diagnosis and future implications.

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Management of a Patient with RBD

23

Michael J. Howell

23.1 Introduction

The spectrum of dream enactment in RBD ranges from benign hand movements to violent life-threatening behaviors. The primary management goal is to prevent sleep-related injury. Thus, educating a newly diagnosed patient and the bed partner about the potential dramatic adverse consequences is an important first step, as subsequent measures ranging from environmental modification to the treatment of comorbid sleep disorders and the pharmacotherapy of RBD will depend upon their adherence and follow-through.

If concerning dream enactment persists once ancillary sleep disorders are treated and RBD-inducing medications (primarily SSRIs and venlafaxine) are minimized or discontinued, then medication therapy is reasonable. The most commonly employed agents include clonazepam or melatonin taken orally at bedtime. However, clinicians should be aware that the evidence supporting these therapies is primarily based upon case series, small clinical trials, and expert consensus.

As RBD is often a prodromal syndrome of alpha-synuclein pathology, management should include monitoring for neurodegeneration. This includes careful clinical follow-up for subtle abnormalities of movement and cognition. Additionally, patients should be provided with a disease risk assessment and counseling for what is often a sobering discovery. Finally, interested patients should be offered the opportunity to participate in research, as an international network of RBD investigators is currently developing protocols for clinical trials of disease-modifying (neuroprotective) agents. For these RBD patients, enrollment in translational research can be empowering as they deal with the likely prospect of developing a neurodegenerative disorder.

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23.2 Environmental Safety

RBD can result in bruising, lacerations, and fractures to both patients and bed partners. Over 11% of RBD patients have had injuries requiring medical attention or hospitalization [1]. Severe neurological injury can result from epidural or subdural hematomas as well as cervical or other spinal fractures. Elderly RBD patients at high risk include those with osteoporosis or those on anticoagulant medications. Additionally, there is a long list of medical vulnerabilities that can lower the threshold for severe RBD-related injuries [2].

Thus environmental modification is a critical early intervention in all patients with RBD. Any potentially dangerous items that could be picked up, swung, or thrown should be removed. These can include such seemingly benign objects as an alarm clock or lamp. To inquire about the bedroom environment, a clinician can ask an open-ended question such as. "What are the items in your bedroom that could potentially injure you or your bed partner?"

Considering the widespread prevalence of firearms (over 300 million) in the United States [3], a special consideration needs to be made to screen for guns, particularly handguns, in the bedrooms of the United States. Given the potential fatal consequences of discharging a firearm during dream enactment, it is critically important that guns (and other weapons, such as knives) be removed from the bedroom.

In cases where patients have previously stood or exited the bed (both high-risk behaviors), strenuous efforts should be made to minimize potential injury. Options include sleeping bags or bed rails to prevent the patient from leaving the bed, removing the box spring and bedframe to sleep on a solitary mattress, or a pressure-sensitive bed alarm with a friendly voice recording directed to calm the patient during vigorous dream enactment [4].

Adherence to these interventions will vary and may require repeated discussions to convince a patient that these measures are necessary. It is important for patients to understand that even rare dream enactment behavior can result in potentially life-threatening injury [1].

23.3 Managing Ancillary Sleep Disorders

Under normal physiological conditions, REM sleep is characterized by vivid mentation combined with skeletal paralysis that prevents dream enactment. REM sleep fragmenting disorders can lead to RBD-like behaviors as abrupt cortical arousals suddenly unleash previously suppressed dream enactment. The three most common pathologies that mimic RBD are obstructive sleep apnea (OSA), severe periodic limb movement disorder, and orexin deficiency causing Narcolepsy type 1. Addressing these conditions can minimize potentially injurious behaviors.

OSA, a collapse of the upper airway during sleep, is most pronounced during REM sleep. Because of this phenomenon, many OSA patients will suddenly awaken from a dream, often with a gasp, while striking or lashing out. This is known as

"OSA pseudo-RBD" [5]. Dream mentation may include a theme of drowning or being choked by an assailant. In these cases, preventing upper airway collapse with either positive airway pressure, dental appliance, or upper airway surgery typically resolves the abnormal behaviors. When dream enactment persists despite effective OSA treatment, it is appropriate to pursue a repeat in-laboratory polysomnogram to evaluate for the persistence of REM motor activity, i.e., loss of REM atonia, despite the correction of sleep-disordered breathing.

Periodic limb movements (PLMs) are a recurrent triple-flexion (dorsiflexion of the foot, knee flexion, and hip flexion) response of the lower extremities. When correlated with non-restorative sleep, a patient is considered to have PLM disorder (PLMD) . Occasionally PLMs can be robust, even injurious, and thus mimic the motor activity of RBD, especially when there is simultaneous dream enactment. Furthermore, while the stereotyped motor activity of PLMs typically arises out of NREM sleep, it can persist into REM sleep. Distinct from RBD however, injurious PLM activity can be typically resolved, including control of dream-enacting behavior, with dopaminergic therapy [6].

These pseudo-RBD disorders, due to OSA and/or PLMD, are distinguished from RBD as their behavior is a REM-related motor event that arises during an arousal out of REM sleep, while RBD is a within-REM sleep motor and DEB disorder.

Narcolepsy is a disorder of sleep-state stability. It is caused by a deficiency of the neurotransmitter orexin, and affected individuals will experience sudden fluctuations between wake and sleep phenomena. Patients describe not only daytime sleepiness but also nighttime sleep fragmentation (unable to consolidate sleep), sleep-related hallucinations (REM mentation intruding into wakefulness), sleep paralysis (REM paralysis persisting into wakefulness), and cataplexy (intrusion of REM atonia triggered by an emotional stimulus). Approximately half of narcolepsy patients experience excessive REM sleep motor tone (intrusion of wakeful motor activity during REM sleep) [7–9]. Because of this, many patients with narcolepsy describe dream enactment, although patients are typically younger and the dream enactment less violent than in the idiopathic form of RBD [9]. Bedtime therapy with sleep-consolidating agents, such as clonazepam or sodium oxybate, has been anecdotally reported to be effective. However, further studies are clearly needed to better understand the optimal treatment of dream enactment in the setting of narcolepsy [10]. For further discussion of RBD in narcolepsy-cataplexy, please refer to Chap. 11.

23.4 Managing Medications That Induce (or Possibly Unmask) RBD

Dream enactment behaviors may arise after initiating neuropsychotropic medications, in particular the antidepressants such as the serotonin-specific reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, mirtazapine, tricyclics or tetracyclics, and monoamine oxidase inhibitors [11]. The exact triggering mechanism is uncertain, but the most likely candidate neurotransmitter is serotonin as the serotonin-producing raphe nucleus modifies REM sleep [12].

Drug-associated RBD is common and considering the widespread use of these medications may represent the most prevalent cause of dream enactment, particularly among the young (see Clinical Case 23.1). One study demonstrated increased REM motor activity in 10% of all depressed subjects who were started on sertraline, a SSRI [13].

When dream enactment clearly presents after a patient initiates an antidepressant, consider initiating a discussion with the treating psychiatrist (or other treating physician) about switching to a different agent, preferably one with a different mechanism of action. However taking into consideration the widespread use of serotonin-based agents, this is often challenging. One antidepressant, bupropion, is by consensus considered an antidepressant least likely to induce dream enactment. This is due to its unique mechanism of action, viz., norepinephrine-dopamine reuptake inhibition, lacking any serotonergic effect and the absence of any published case suggesting a link with RBD [12–14]. Additionally, a clinician should consider recommending, in clinically appropriate cases, the maximal use of non-pharmacological therapy, e.g., psychotherapy, for mental illness. Among cases of persistent dream enactment despite antidepressant dose reductions, switching antidepressants, or eliminating antidepressant medications, RBD pharmacotherapy could be started with either melatonin or clonazepam.

Of note, there is considerable debate as to whether antidepressants induce dream enactment directly through a toxic effect or whether they are merely unmasking dream enactment in an individual who would ultimately have developed RBD even in the absence of a serotonergic medication. Recent evidence suggests that patients with medication associated RBD also have other prodromal markers of neurodegeneration such as anosmia, constipation, and decreased brain dopamine on PET imaging [15, 16]. These findings imply that antidepressant medications are not causing RBD in isolation but instead identify individuals with early alpha-synuclein neuropathology. For further discussion of RBD and antidepressant medications, please refer to Chap. 10.

Clinical Case 23.1

A 32-year-old female presents with a 6-month history of nightly dream enactment. According to her bed partner, the patient's new sleep behaviors include shouting, thrashing, punching, and kicking. These behaviors are short-lived, lasting only a few seconds, and occur predominantly in the latter half of the night. Neither the patient nor bed partner has had a sleep-related injury.

These events began soon after starting fluoxetine to treat a mood disorder. She indicates that while fluoxetine did improve her mood, she would like to consider switching to another antidepressant medication.

She has no Parkinsonian motor symptoms, reports that her sense of smell is intact, but does indicate that she has struggled with constipation for most of her adult life.

The only other medication she takes is hormonal contraception.

Family history is significant only for cardiovascular disease, with no history of neurodegeneration.

Her neurological examination is normal, without resting tremor, bradykinesia, or cogwheel rigidity. Her gait appears normal with a good turn and arm swing. She walks without freezing. Objective olfactory testing was not performed.

In-laboratory video polysomnography demonstrated hand and finger movements during REM sleep suggestive of dream enactment (she appeared to be pointing). Transient REM motor activity was most prominent during the final period of REM sleep. No other sleep-related abnormality was identified.

She was diagnosed with medication-associated RBD and switched from fluoxetine to bupropion. Bupropion was well tolerated and controlled her mood disorder. Dream enactment also diminished, but did not fully resolve as she reported still having weekly episodes. Therefore, she was advised to start bedtime oral melatonin, which at 6 mg fully resolved the dream enactment behaviors.

23.5 Medication Therapy for RBD

If dream enactment behavior persists once ancillary sleep disorders have been treated and any putative offending medication minimized or withdrawn, it is reasonable to consider medication therapy for RBD, which is most appropriate in situations where there is a high risk of sleep-related injury. These cases include patients (or bed partners) with a history of osteoporosis, coagulopathy, anticoagulant use, etc., or who have been hospitalized or sought medical attention for a sleep-related injury. Even in the absence of previous sleep-related injury, concerning behavior that warrants more aggressive management includes either standing up or exiting the bed during dream enactment [17].

In the absence of potentially injurious behaviors and/or comorbidities that increase the risk for sleep-related injury, conservative observation (without pharmacotherapy), with environment safety measures, is reasonable as long as it is paired with clinical follow-up.

The most commonly prescribed[1] agents for the treatment of RBD are clonazepam and melatonin. While the vast majority of RBD reports suggest that either one

[1] For the purposes of this review, melatonin is considered a medical therapy despite being considered a nutritional supplement available over the counter in the United States. It is a biological compound with pharmacokinetic properties that has been demonstrated to be effective compared to placebo in sleep and circadian rhythm disorders. In addition, numerous countries in the European Union and Canada classify melatonin as a medication and require a prescription for its use.

or both of the agents in combination are reliably effective therapies, it is important for physicians, patients, and bed partners to be aware that the evidence supporting their efficacy is limited [18, 19]. Their use has emerged from published case reports, case series, small clinical trials, and expert consensus. Clearly further research in RBD therapy is needed, in particular large, randomized placebo-controlled trials. However, serious ethical issues are raised by the prospect of such studies, mainly involving RBD patients with injurious dream enactment who would be receiving a placebo, as discussed [20]. For further discussion of these and other RBD therapies, refer to Chaps. 24 and 25.

23.6 Monitoring for Neurodegeneration

By the time most RBD patients come to clinical attention, they have already developed other, often subtle, symptoms such as hyposmia and constipation [17]. It is the combination of findings that indicates a more diffuse neuropathology, and it helps a clinician confirm (as well as explain to the patient) that this sleep disorder is part of a larger and evolving neurological syndrome. Neuropsychological examination and other testing may reveal impairments in executive function, color identification, and/or visual-spatial tasks; however, these deficits often go undetected in routine clinical evaluations [12, 17].

As RBD is considered to be a prodrome of alpha-synuclein pathology, prospective long-term clinical follow-up is necessary. Once dream enactment behavior has been addressed, patients should meet with a clinician who can perform a detailed neurological evaluation at regular intervals, at least annually, to be screened for movement and cognitive deficits.

At each visit patients should be queried for bradykinesia and resting tremor. Common bradykinetic symptoms include taking longer to eat, dress, or walk through a store. However, patients may have limited insight and assume that their slowness is similar to their middle-aged or elderly peers. Because of this, a secondary observer, such as a family member or companion, can be a valuable resource when screening for bradykinesia. In regard to resting tremor, it should be noted that RBD is linked with the non-tremor predominant subtype of Parkinson's disease which is easily missed in the early stages [21, 22]. Further, even when the oscillations are present, they may go unrecognized, as a resting tremor is by definition not functionally limiting [17].

RBD predicts the development of freezing of gait (FOG), a disabling condition poorly treated with conventional dopamine-based Parkinson's disease therapies [22, 23]. FOG is characterized by transient episodes of absent forward movement during ambulation most commonly noted during gait initiation or turning. FOG can be screened with a single question, "Do your feet ever feel as if they are stuck to the floor?" FOG is important to identify as interventions, such as physical therapy and assistive devices (canes, walkers), can prevent falls. For further discussion of gait and postural disorders in RBD, please refer to Chap. 38.

Subsymptomatic Parkinsonism can often be elicited on examination. A clinician should scrutinize a patient's affectation, blink rate, speed of articulation, and motor tone (with distracting maneuvers in the opposite extremity to extract subtle cogwheel rigidity). Gait testing can detect arm swing asymmetry, bradykinetic strides, excessive steps per turn, and FOG. Postural instability is common in the non-tremor predominant subtype of Parkinson's disease and can be tested by sudden retropulsion that normally elicits a righting reflex. However, great care should be taken with this test as the full weight of a patient may suddenly fall back on the clinician (see Clinical Case 23.2). The Unified Parkinson's Disease Rating Scale provides quantified assessments of these examinations and is a useful tool in the prospective evaluation of RBD patients. Cognitive screening and monitoring can be conducted with the Montreal Cognitive Assessment [17].

Clinical Case 23.2

A 62-year-old male RBD patient presents with imbalance. He states that he has fallen on several occasions in the last year, and with a history of osteoporosis, he is concerned about traumatic fractures.

He was diagnosed with RBD 2 years prior after a 15-year history of dream enactment and a polysomnogram that confirmed excessive transient and tonic REM motor activity. His parasomnia has been under good control with 12 mg of melatonin along with bedroom modification. He was diagnosed with mild Parkinson's disease last year with bradykinesia and cogwheel rigidity that clearly improved with carbidopa/levodopa therapy.

When asked about gait freezing, he indicates that yes, he often gets "stuck" particularly in restaurants when he has to navigate his feet around chairs and tables.

On examination (2 h after taking carbidopa/levodopa), the patient has only mild bradykinesia and cogwheel rigidity in the right upper extremity. Tremor was not elicited on examination even with distracting maneuvers. Gait testing revealed subtle decreased arm swing on the right. However, when testing sudden retropulsion, the 100 kg patient had no reflexive righting response and fell backward onto the examiner who struggled but managed to catch him.

The patient and his family were educated on the nature of his imbalance and he was referred to physical therapy. Several Parkinson's disease medications were initiated but his gait freezing and postural instability persisted.

23.7 Counseling and Neuroprotection

RBD is a fearsome diagnosis for many patients. While medications can control dream enactment, the prospect of an impending neurodegenerative disease is a frightening and often overwhelming discovery. Physicians can help lessen the shock of the diagnosis by building rapport with empathy and education.

The greatest concerns for most patients are the prospect of impending disability and the unknown impact the disease may have upon family and finances. With a careful clinical evaluation, the physician can define a patient's risk profile and determine those who are likely to convert to Parkinson's disease (or related condition) in the midterm (within the next 5–10 years). In particular, hyposmia, constipation, impaired color vision, sleepiness, orthostatic hypotension, and subtle motor and/or cognitive dysfunction in the absence of antidepressant medications place RBD patients at high risk of converting to a diagnosable neurodegenerative disease. Stratification with these markers increases the risk of conversion by 200% [24]. Conversely, the absence of these findings suggests that a patient may be reassured that conversion is more likely remote.

RBD among younger adults, those less than 50 years of age, is most often due to either an RBD-associated medication or associated with narcolepsy. It is uncertain whether these individuals have the same risk for neurodegeneration as older RBD patients (see Sects. 23.3 and 23.4 above). It is suspected that their risk of conversion is lower; however it should be noted that parkinsonian disorders can emerge as late as half a century after the onset of RBD [25]. Thus, even young patients should be screened for other early features of neurodegeneration (anosmia, constipation) and carefully followed with serial neurological examinations.

Importantly, patients should be informed that the most common future disorder, Parkinson's disease, is a treatable condition, and a brief summary of what comprises PD and related disorders should be stated. Numerous medications, surgical procedures, and rehabilitative therapies can help patients maintain a high level of independent function that can last for many years. Additionally, patients and their families should also be advised to watch for symptoms of dementia with Lewy bodies. This disorder of progressive cognitive impairment is distinguished from Alzheimer's disease by a fluctuating course and visual hallucinations. Unfortunately, unlike PD, therapeutic options for DLB are limited. An important consideration in regard to what and how this topic should be communicated and discussed is the level of education and medical sophistication, and personality style, of the patient and spouse.

RBD patients often wonder about possible neuroprotective interventions. At the current time, there are no proven neuroprotective therapies in RBD. Aerobic exercise may be disease modifying in Parkinson's disease but results are mixed [26, 27]. However, considering the clear cardiovascular and mood benefits of exercise, it is reasonable to recommend a routine of aerobic activity (>30 min at least 3 times per week) in nearly all individuals. For a further discussion of neuroprotection and potential disease modification, please refer to Chap. 44.

As numerous scientific investigations are currently underway, RBD patients should be offered the opportunity to participate in clinical trials. Many patients describe a feeling of empowerment, even in the absence of a discovery that directly affects them, by participating in a process that benefits future generations. A multinational consortium of investigators, the International Rapid Eye Movement Sleep Behavior Disorder Study Group (IRBDSG), is a resource for patients interested enrolling in clinical trials [20]. An ultimate goal of the IRBDSG is to identify

disease-modifying therapies that could slow or halt the progression from iRBD to overt neurodegeneration or cure emergent Parkinson's disease and related disorders. For further discussion of the IRBDSG, please refer to Chap. 3.

Finally, RBD offers patients, and their physicians, a unique and valuable perspective. There should be enhanced appreciation for the intact brain function we have while we have it. Our ability to move, to think, and to feel spontaneously is a wondrous marvel, but ultimately these delights are transient. Because of this situation, a diagnosis of RBD presents an opportunity to initiate or accelerate activities (such as taking a foreign trip, climbing a mountain, hiking around national parks, etc.) often imagined but never adequately completed. Most importantly it is a reminder that we should express the appreciation and affection we have for those with whom we share our lives.

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Melatonin Therapy of RBD

24

Dieter Kunz and Frederik Bes

24.1 Introduction

In 1995 we used melatonin as a treatment for rapid eye movement (REM) sleep behavior disorder (RBD) for the first time [1]. A 64-year-old man with the clinically and polysomnographically (PSG) confirmed diagnosis of RBD also suffered from insomnia (having troubles with both initiating and maintaining sleep) with excessive daytime tiredness and impairment of short-time memory. Due to the patient's comorbidity, clonazepam was not considered to be a good initial treatment option, and so melatonin therapy was begun with a dose of 3 mg within 30 min before bedtime. Surprisingly, over weeks not only general sleep abnormalities and cognitive/amnestic deficits but also the RBD symptoms showed a complete clinical recovery. A second PSG study after 2 months of treatment showed no major changes in sleep structure, except an increase of REM sleep (13% vs. 17% of sleep period time) and a better qualitative preservation of REM sleep-associated muscle atonia with a reduction of REM epochs with movement time to almost half of the baseline. Actigraphic data showed that in the first 2 weeks of melatonin treatment, movement parameters during time in bed generally decreased to about 70% of baseline value and that after 5 months of treatment, these parameters were reduced even further to about 40% of baseline value. Clinical symptoms gradually returned 3 weeks after the end of treatment starting with yelling and a first episode of jumping out of bed 3 months after melatonin discontinuation. Thereafter, treatment was resumed.

In this chapter, we summarize our own experience and the cumulative published data on the treatment of RBD patients with melatonin and melatonergic agonists. Also we cite evidence for our hypothesis that one basic mode of therapeutic action is on the influence of melatonin on RBD symptoms via the circadian timing system.

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24.2 Melatonin and Melatonergic Agonists: Actions and Metabolisms in the CNS

Looking into the physiology, melatonin, *N*-acetyl-5-methoxytryptamine, first isolated 1958 by Lerner and colleagues in bovine pineal glands, is a product of tryptophan metabolism [2]. It is mainly secreted by the pineal gland but also produced by other tissues, such as the retina, lymphocytes, and gastrointestinal tract.

Melatonin release follows a marked circadian rhythm, controlled by the hypothalamic suprachiasmatic nucleus (SCN) as the central circadian pacemaker or master clock. The SCN receives its timekeeping input mainly from the retinohypothalamic tract.

Special photoreceptive retinal ganglion cells, containing the photopigment melanopsin, are involved in the projection from the retina. Highest melatonin levels occur during the night and transduce the information "darkness" as a feedback signal to the SCN, for readjusting the clock [3], and to other inferior central and peripheral circadian oscillators.

Melatonin has high accessibility throughout the body due to its amphiphilic nature. It exerts its physiological effects through activation of at least two high-affinity G-protein-coupled receptors MT_1 and MT_2, which show distinct molecular structures, pharmacological characteristics, and anatomical distribution patterns. Tissues with MT_1 and MT_2 receptors include the retina, cerebral cortex, hypothalamus, midbrain, periaqueductal gray, cerebellum, hippocampus, ovaries, cerebral and peripheral arteries, kidneys, pancreas, adipocytes, and immune cells [4, 5]. Cerebral tissues with mainly MT_1 receptors include the SCN, pituitary gland pars tuberalis, habenula, dorsal raphe nucleus, superior colliculi, and substantia nigra pars compacta; those with mainly MT_2 receptors include the reticular thalamic nucleus, inferior colliculi, and substantia nigra pars reticulata [5]. Physiologically, MT_1 and MT_2 receptors have distinctive functional roles. In rodents, circadian phase shifting is preferentially mediated through activation of the MT_1 receptor, as demonstrated using MT_1 knockout mice in a model of circadian re-entrainment [6]. It has been shown that MT_1 may also modulate biological clock-related gene expressions, as the expression of most clock genes in the pituitary gland is reduced in MT_1 knockout mice but not in MT_2 knockout mice [7]. Additional evidence exists that melatonin action in the SCN can be attributed to mainly MT_1 receptors with only a minimal role for MT_2 [8]. Further experiments with MT_1 and MT_2 knockout mice indicate that each melatonin receptor subtype differently regulates the vigilance states: MT_2 receptors mainly non-rapid eye movement (NREM) sleep and MT_1 receptors mainly REM sleep [9].

Phase and amplitude of SCN neuronal activity rhythm can be alternately stimulated by light and melatonin just like a clock pendulum [10]. The involvement of melatonin in circadian regulation can not only be observed on the cellular and neuronal level but also in the modulation of a wide variety of highly relevant physiological functions [11, 12]. Besides the well-known chronobiotic and sleep-facilitating properties in diurnal species, many other physiological effects have been attributed to melatonin, such as modulation of other hormone secretions and enhancement of

immunological functioning. Other functions of melatonin include anti-inflammatory, cancer protective, glucose regulatory, and neuroprotective, as well as free-radical scavenging and antioxidant properties [13, 14].

Orally administered melatonin has a short half-life of approximately 1 h and a low bioavailability of 15% [15]. It is well tolerated without significant side effects, even up to very high doses. In a phase I dose escalation study in healthy volunteers to assess the tolerability and pharmacokinetics of 20, 30, 50, and 100 mg oral doses of melatonin, no adverse effects other than mild transient drowsiness with no effects on sleeping patterns were seen [16]. Circulating melatonin is metabolized in the liver, mainly by the cytochrome P450 enzyme CYP1A2, to its primary metabolite 6-hydroxymelatonin and after conjugation with sulfate excreted in urine. Decreased CYP1A2 activity in the liver either genetically determined or from concomitant medication, hence, can slow down melatonin metabolism. The proportion of individuals with a slow CYP1A2 phenotype is about 13% [17] but may vary among ethnic populations. With patients who are slow metabolizers in this respect, the ingestion of the usual doses of exogenous melatonin can thus result in accumulation and, by consequence, to loss of its circadian variation, which eventually leads to a loss of effectiveness [18]. Decreasing the dose or intermittent melatonin administration every other day can remedy this.

During the last decade, the therapeutic potential of melatonin in a wide variety of clinical conditions has become an area of great interest, leading to the development of new agents, including prolonged-release melatonin and selective melatonin receptor agonists.

Prolonged-release melatonin (Circadin®) was approved in Europe by the European Medicines Agency (EMA) 2007 as monotherapy for the short-term treatment of primary insomnia in patients of 55 years and over and is currently commercialized in Europe and Asia-Pacific territories [19]. Agomelatine (Valdoxan®) is a melatonin MT_1 and MT_2 receptor agonist, and a weak 5-HT_{2C} antagonist received marketing authorization in the European Union in 2009 and Therapeutic Goods Administration (TGA) approval for marketing in Australia in August 2010 for the treatment of depression, whereas the development for the US market was discontinued in October 2011 [19, 20]. Ramelteon (Rozerem®) is a melatonin MT_1 and MT_2 receptor agonist, which has been approved by the US Food and Drug Administration (FDA) 2005 for the treatment of insomnia [19, 20]. Tasimelteon (Hetlioz®) is another selective agonist for the melatonin receptors MT_1 and MT_2, approved by the FDA and since 2015 in Europe by the EMA solely for the treatment of non-24-h sleep-wake disorder [19, 21].

24.3 Melatonin and Melatonergic Agonists as Treatment Options for RBD

Our first findings were confirmed in an open-labeled trial with six patients (melatonin 3 mg within 30 min before bedtime) and also in a randomized, double-blind, placebo-controlled trial in a crossover design with eight patients (placebo or

melatonin 3 mg within 30 min before bedtime), each for a period of 4 weeks [22, 23]. The diagnosis of RBD was confirmed clinically and with time-synchronized video-PSG (vPSG). Twelve of 14 patients showed a clear clinical improvement within weeks. Eleven patients no longer experienced enacting of dreams. Another responder reported a reduction of RBD episodes from every night to once a week only. None of these responders reported any frightening dreams during melatonin treatment. After discontinuation of melatonin, RBD symptoms returned only in some patients after weeks to months. The electromyogram (EMG) of the PSG at the end of melatonin treatment showed significantly decreased REM sleep without atonia (RWA; from 32% down to 11% [22] and from 39% down to 27% [23]), while phasic activity during REM sleep was unchanged. Interestingly, in the placebo-controlled crossover study, we nevertheless found a better preservation of muscle atonia at the end of the placebo phase, but only in those patients who were treated with melatonin in the earlier verum phase. Due to the crossover design, the control vPSG for those patients was performed 5 weeks after discontinuation of melatonin treatment. Apparently melatonin effects persist after treatment discontinuation, which might have some clinical relevance.

Since then, a few more case reports, small case series, retrospective case reviews, and one randomized, placebo-controlled crossover study on the efficacy and tolerability of melatonin and melatonergic agonists for the treatment of RBD have been published (summarized in Table 24.1 for melatonin and in Table 24.2 for melatonergic agonists).

Anecdotal evidence for melatonin effects on RBD is provided by a prospective observational study performed by Takeuchi et al. [24]. They examined effects of melatonin in 15 patients with vPSG confirmed RBD, but without provision of further information regarding comorbidities, including possible obstructive sleep apnea (OSA), or duration of melatonin treatment and follow-up. Melatonin dose was 3–9 mg administered 30 min before bedtime. Thirteen patients reported a mild to strong improvement of symptoms. The authors reported a dose dependency of observed effect in some patients without providing further data. In the melatonin responders, efficacy was investigated by vPSG. Melatonin administration significantly reduced the percentage of tonic REM activity (from 16 to 6%) while leaving all other sleep variables in vPSG unchanged. In addition, drug levels were measured at baseline and at 3 h after administration. The investigators found a higher response in patients with lower baseline melatonin levels.

In a retrospective observational study, Boeve et al. confirmed the efficacy of melatonin monotherapy as well as combined therapy with clonazepam. They examined 14 selected patients with "RBD associated with several neurologic conditions," after clonazepam either had failed, showed significant side effects, or was contraindicated [25]. One half of the patients still took clonazepam (0.5–1 mg/night) in addition to melatonin; the other half converted to melatonin monotherapy. Ten patients showed marked clinical improvement, five of them combined with clonazepam. The melatonin responders showed an improvement concerning nightmares, which tended to correlate with the improvement in dream enactment behaviors. The effective dose of melatonin ranged from 3 to 12 mg taken at bedtime. Side effects

Table 24.1 Effects of melatonin on RBD symptoms

Author	Study type, diagnostic criteria	*N*	Patient population, concomitant diseases	Treatment, dosage, duration	*N* responding (based on patients and bedpartners' reports)	vPSG
Kunz et al. (1997) [1]	Case report, ICSD-2	1	64 y-old male, iRBD	Melatonin 3 mg per night, 5 months	1	↑%REM sleep, ↓RWA and ↓phasic EMG levels in REM
Kunz et al. (1999) [22]	Case series, ICSD-2	6	Three males, mean age 54 y, range 26–71 y, one PD, three of six with memory and concentration deficits	Melatonin 3 mg per night, 6 weeks	5	Significant ↑ REM atonia, significant ↓ stage shifts + MT in REM epochs
Kunz et al. (2010) [23]	RCT, crossover design, ICSD-2	8	Eight males, mean age 54 y, range 26–67 y, two narcolepsia, one PD	Placebo/melatonin 3 mg for 4 weeks, switch from the placebo to verum group or vice versa for another 4 weeks	7, significant improvement in CGI	Significant ↓ of RWA in the melatonin group, extended beyond the placebo part, if melatonin given first
Takeuchi et al. (2001) [24]	Case series, ICSD-1	15	Fourteen males, mean age 63.5 y, RBD with no further disclosures	Melatonin 3–9 mg per night, duration NM	13	↓Tonic REM activity
Boeve et al. (2003) [25]	Retrospective review, ICSD-R	14	Thirteen males, median RBD onset age 56 y, range 22–77 y, seven LBD, two MCI, two narcolepsia, one PD	Melatonin 3–12 mg per night +/− clonazepam 0.5–1 mg in seven patients, duration NM	10, 5/10 patients with concomitant clonazepam	ND

(continued)

Table 24.1 (continued)

Author	Study type, diagnostic criteria	*N*	Patient population, concomitant diseases	Treatment, dosage, duration	*N* responding (based on patients and bedpartners' reports)	vPSG
Anderson et al. (2009) [32]	Retrospective review, ICSD-2	2/39[a]	Thirty-eight males, mean age 66 y, range 34–86 y, one MCI + mild OSA	Melatonin 10 mg per night in 2/39 patients, 20 months. 37/39 other drug therapies	2	ND
McCarter et al. (2012) [26]	Retrospective review, ICSD-2	27/45[a]	Thirty-five males, mean age 66 y, range 29–86 y, 10 PD, 6 MCI, 5 MSA, 3 LBD, 30 OSA, 13 comorbid depression	Melatonin 6 mg per night in 25 patients, + clonazepam 0.5 mg in 2 patients, clonazepam monotherapy in 18 patients, 27.4 ± 24 months	17 (68%) improvement on melatonin, vs. 89% on clonazepam, melatonin ↓ injuries significantly	ND
Lin et al. (2013) [27]	Retrospective review, ICSD-2	28	Twenty males, 66.5 ± 9 y, 10 PD, 16 with OSA, 6 with cognitive decline	Melatonin 3–6 mg per night for 4 months, then +0.5–3 mg clonazepam	26 at 6 mg in monotherapy	Decrease of WASO and EMG bursts during total REM time
		Đ: 101			Đ: 81	

Abbreviations: *CGI* Clinical Global Impression rating scales, *LBD* Lewy body dementia, *EMG* electromyogram, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *ISCD-R/1/2* revised/first/second edition of the *International Classification of Sleep Disorders*, *MCI* mild cognitive impairment, *MSA* multiple system atrophy, *MT* movement time, *ND* not done, *NM* not mentioned, *OSA* obstructive sleep apnea, *PRBD* probable RBD, *PD* Parkinson's disease, *RCT* randomized controlled trial, *REM* rapid eye movement, *RWA* REM sleep without atonia, *vs.* versus, *VAS* visual analog scale, *WASO* wake after sleep onset, *y* years, ↑ increase, ↓ decrease, % percent

[a]Group members received several drug therapies

Table 24.2 Effects of melatonergic agonists on RBD symptoms

Author	Study type, diagnostic criteria	*N*	Patient population, concomitant diseases	Treatment, dosage, duration	*N* Responding (based on patients and bedpartners' reports)	vPSG
Bonakis et al. (2012) [28]	Case review, NM	3	iRBD	Agomelatine, 25–50 mg per night, 6 months	3 (1 at 25 mg, 2 at 50 mg)	Significant ↓of %REM epochs with high tonic density
Nomura et al. (2013) [29]	Case series, ICSD-2	2	59 y-old male, 76 y-old female, 1 PD, 1 MSA + OSA	Ramelteon 8 mg monotherapy in 1 patient, + clonazepam 1 mg in 1 patient, 2–3 y	2, 1 with rebound after discontinuation	↓in % RWA
Esaki et al. (2016) [30]	Open-labeled trial ICSD-2	12	iRBD	Ramelteon 8 mg daily, at least 4 weeks	Unclear, contradictory results, a trend toward significance on VAS	No statistically significant effect on RWA, RBD severity scale, and all other sleep parameters
Kashihara et al. (2016) [31]	Open-labeled trial ICSD-2	35	PD, sleep disorders 24 with PRBD	Ramelteon 8 mg daily, 12 weeks	Unclear, ↓scores in the Japanese RBD questionnaire	ND
		Đ: 52			Đ: unclear	

Abbreviations: see Table 24.1

were dose dependent and led to withdrawal in one patient (morning sleepiness with 9 mg melatonin and 0.5 mg clonazepam). All patients had used other psychoactive medications (donepezil, selective serotonin reuptake inhibitors (SSRI), carbi-/levodopa, psychostimulants), with no significant improvement of RBD frequency or severity. No details were given as to a possible deterioration of symptoms due to co-medication or to other co-medications such as beta-blockers.

McCarter et al. [26] retrospectively reviewed efficacy and side effects, particularly injury frequency under melatonin and clonazepam treatment among 45 patients with PSG confirmed RBD. Coexisting neurodegenerative disorders were seen in 24 patients, and almost all patients took antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRI) or SSRIs and dopaminergic and anticholinergic agents. Furthermore, 30 patients (67%) had moderate OSA, with a group median apnea-hypopnea index (AHI) of 9 (range 5–68; the authors did not report how many

of them were actually treated for OSA). Grade of severity of RBD was similar with or without neurodegenerative diseases, OSA, and concomitant medication. Twenty-five patients received melatonin, 18 received clonazepam, and 2 received both as initial treatment. The median effective dose was 6 mg for melatonin and 0.5 mg for clonazepam. Melatonin showed an overall improvement in 68% of patients, clonazepam in 89% of patients, but melatonin-treated patients reported significantly reduced injuries and fewer side effects. Efficacy of both medications was comparable, regardless of the presence or absence of comorbid neurodegenerative disorders. Eight patients switched from monotherapy with melatonin or clonazepam to a combination of both, without further improvement. The authors substantiated an association between antidepressant use and RBD frequency. Patients treated with clonazepam reported more frequent side effects than those treated with melatonin, a group difference trending toward statistical significance. Side effects associated with melatonin treatment were sleepiness (29%), trouble thinking (12%), unsteadiness (8%), nausea (8%), sexual dysfunction (8%), and dizziness (4%), each of these was most frequently rated to be mild in severity. However, the study was retrospective and had some methodological problems, so the results must be interpreted with considerable caution.

In another retrospective study, Lin et al. [27] evaluated the data from 28 patients with PSG confirmed RBD. Ten patients also showed symptoms of Parkinson's disease (PD), and four other patients exhibited cognitive decline. Patients with OSA were first successfully treated with nasal continuous positive airway pressure (CPAP). Then, all patients received melatonin, 2 patients at a dose of 3 mg nightly and 26 patients at a dose of 6 mg nightly. After 8 weeks taking a dose of 3 mg, the reports of the two patient's bed partners indicated no relevant change in extent and frequency of abnormal behaviors, nor did follow-up PSG show reduced EMG activity in REM sleep. However after 4 months treatment with 6 mg melatonin nightly, the other 26 patients showed a clear clinical improvement with significant reduction of nights with dream enactment behavior. After the first period of melatonin monotherapy, all patients began a combination therapy with clonazepam 0.5–1 mg per night. Abnormal behaviors in sleep improved but did not persist in the group with melatonin 3 mg in combination with clonazepam 0.5–1 mg nightly, so finally melatonin was increased to 6 mg. The group treated with 6 mg melatonin first and subsequently combined with clonazepam showed a significant reduction in the percent of WASO compared to baseline. The authors did not provide details to treatment-related side effects.

Only a limited number of studies have examined the efficacy of melatonergic agonists in RBD. One case series [28] described the positive effects of agomelatine in three patients with clinical and PSG confirmed idiopathic RBD (iRBD). One month after initiation of treatment with 25 mg per night, aggressive behavior had fully remitted in one patient. The other two patients, still reporting some episodes of shouting and jerking, increased the dose to 50 mg per day. This led to further improvement with clearly reduced numbers of RBD episodes by the end of the follow-up period. All patients recalled fewer dreams, and their dream content changed dramatically, turning more pleasant. After 6 months of treatment, vPSG confirmed

a trend for improved sleep efficiency and a significant decrease of REM epochs with high tonic density. Agomelatine was well tolerated and no side effects were reported.

Ramelteon has been more frequently reported in RBD therapy. Nomura et al. [29] treated two patients with symptomatic RBD with ramelteon 8 mg/night. The first patient received ramelteon in monotherapy due to contraindications for the use of clonazepam, and the other was co-administered ramelteon because of failed effectiveness with clonazepam. Both patients improved clinically, one of them completely recovered with rarely experienced dreams and with relapsing after treatment discontinuation. Side effects were not mentioned. PSG showed a decrease of RWA as well as of the AHI. An open-labeled trial with ramelteon [30] for the treatment of iRBD showed contradictory results. Twelve consecutive patients received 8 mg ramelteon daily for at least 4 weeks. The treatment did not have a clear effect on RWA or on RBD severity scale measured by vPSG, showing a significant decrease in only two patients. Furthermore, there were no statistically significant differences in all other sleep parameters. Only a visual analog scale provided by the bedpartners showed a trend toward significance. Ramelteon was well tolerated in most patients, but two patients dropped out because of side effects (drug rash, dizziness). Kashihara et al. [31] investigated the effects of ramelteon on sleep disorders, including RBD, in 35 patients with PD. The patients received 8 mg of ramelteon before sleep once daily for 12 weeks. Motor and sleep symptoms were evaluated both before and after ramelteon administration. Twenty-four of the 35 patients enrolled in this study were diagnosed with probable RBD (pRBD) using the Japanese version of the RBD screening questionnaire. Ramelteon reduced the severity of sleep disturbances in patients with PD. It also lowered scores on the Japanese version of the RBD questionnaire in patients with PD and pRBD. Unfortunately, diagnosis and treatment were not verified by PSG.

To date, no studies on the efficacy of tasimelteon for the treatment of RBD have been published.

24.4 Circadian Modulation of REM Sleep

In the discussion of the underlying mechanisms that cause the positive effects of melatonin on RBD, it is crucial to recognize that the drive for REM sleep contains the essential attributes of a circadian process, in addition to its ultradian appearance.

Under usual entrained conditions, the probability to enter REM sleep (i.e., REM sleep propensity) fluctuates systematically within 24 h, being high during the last half of the nightly sleep phase [33]. REM sleep latency depends more on circadian phase than on previous wakefulness duration [34] and shows a clear diurnal variation which suggests a circadian profile [35]. Also, while manipulating the sleep-wake cycle in the presence of a light/dark cycle, the circadian character of the REM sleep rhythm is preserved [36].

In a time cue-free environment, the crest of the circadian REM sleep propensity coincides roughly with the trough and early rising part of the body temperature

circadian rhythm, the latter representing a typical endogenous reference for circadian phase [34, 37]. This temporal relationship is preserved when the timing of the sleep-wake cycle dissociates from the circadian temperature rhythm, either spontaneously [33, 37] or with experimental protocols that force desynchrony between these variables [38, 39].

Animal research supports the notion of circadian REM sleep modulation. Attempts to enter REM sleep increased during REM sleep deprivation and were modulated by circadian phase in rats, but in SCN-lesioned animals, this circadian modulation had vanished [40]. In an elegant experiment with the crepuscular mammal *Octodon degus* diurnal and nocturnal REM sleep deprivations provoked equivalent amounts of REM sleep debts, but a consistent REM sleep rebound was found only after nocturnal deprivation, which strongly supports the notion that the circadian system actively promotes REM sleep [41].

A circadian modulation of REM sleep logically implies that next to circadian period and phase, REM sleep propensity has (circadian) amplitude and also offsets if the difference between the absolute amplitudes of minimum and maximum was unequal. In our opinion, it is first and foremost the circadian *amplitude* that represents the strength of the REM sleep propensity rhythm. This strength, in turn, would heavily depend on the timely orchestration and integrity of all processes and conditions in the circuitry that controls REM sleep.

24.5 Melatonin, Circadian Timing System, and REM Sleep

While treatment of RBD seems to be effective with exogenous melatonin and, with anecdotal evidence, also with melatonin agonists, the mode of action is still under discussion. We have assumed that this is based on the restoration of the circadian timing system integrity by stabilizing phase and amplitude of the internal clock [42]. Enhancement of the biological clock functioning by melatonin will increase the amplitude of circadian REM sleep propensity, and thus its strength, by improving the timely orchestration and integrity of all underlying processes necessary for a proper functioning of REM sleep. Improvement to a proper functioning of REM sleep might then imply alleviation of RBD symptoms.

Our hypothesis is based on a number of observations. In a randomized double-blind, placebo-controlled study with 14 patients, who were specifically selected on reduced REM sleep amounts (more than 25% below age norm), we could demonstrate that melatonin treatment significantly increased REM sleep percentage, REM sleep continuity, REM sleep polarity (i.e., short REM sleep episodes at the beginning and long REM sleep episodes at the end of the sleep period), and also the amplitude of temperature decline during nighttime sleep [43]. Although several patients in this study were non-RBD, the data demonstrate that, regardless of the underlying pathology, properly administered melatonin can normalize nighttime REM sleep and strengthen circadian amplitude.

Another relevant observation we repeatedly made is that the effects of melatonin slowly develop and clearly outlast the actual period of melatonin administration.

RBD symptoms only gradually return after the melatonin treatment is stopped, sometimes over more than a year. This observation rules out that direct "pharmacological" effects of melatonin on, e.g., body temperature or sleep consolidation would be the cause for its therapeutic effectiveness. Furthermore, we observed in our initial pilot studies with RBD patients that responders and nonresponders were best distinguished by evaluating their sleep hygiene, i.e., stable vs. varying bedtimes and times of melatonin intake [22, 43]. This clinical observation is in agreement with the fact that melatonin receptor sensitivity in the SCN varies with circadian time [44]. As a consequence exogenous melatonin should be administered consistently within a rather narrow time span in order to gain optimal effects. Both observations support our hypothesis that some kind of internal desynchrony is part of the underlying pathophysiology, implying involvement of the circadian timing system.

It might be objected that there is no identified circadian timing abnormality in RBD that has been published up to now. However, RBD may be considered as a powerful predictor, if not a prodromal marker, of neurodegenerative synucleinopathies like PD, Lewy body dementia, or multiple system atrophy, which are mostly accompanied by a substantial breakdown of the circadian system [45–47]. In this respect, disturbed circadian timing system integrity might be the link to RBD as a harbinger of neurodegenerative pathology. In our opinion, signs of circadian disruption are indeed not clearly overt in the early stages, that is, well before conversion to a full-blown synucleinopathy. Initial indications may be only very subtle and faint. But little by little, more and more elements of circadian disruption will inevitably be elucidated over the time course of conversion to synucleinopathy [46]. In our experience melatonin improves RBD symptoms in neurodegenerative disorders, but we observed complete resolution of symptoms only in those patients who had not yet converted to PD [23].

We see further hints of circadian timing system involvement when considering the growing number of reports about the melatonin receptors [44]. In particular, the hypothesized role of the MT_1 receptor in clock-related processes [6–8] and in REM sleep regulation [5, 9] seems to be of relevance. The clinical significance of the melatonin receptors in neurodegeneration is supported by histological postmortem studies. Decreased MT_1 and MT_2 receptor expression have been found in the amygdala and substantia nigra of postmortem tissue from PD patients compared to normal controls, which demonstrates a downregulation of melatonin receptors in regions affected by the disease [48].

Like clonazepam, melatonin might impact directly on REM sleep atonia via modulation of gamma-aminobutyric acid (GABA)-ergic inhibition, as proposed in a publication about a glycine/$GABA_A$-receptor knockout transgenic mouse model of RBD [49]. In PD, melatonin treatment is suggested to prevent neuronal dopamine loss and/or dopamine transporter downregulation via neuroprotective effects. It can ameliorate motor symptoms in experimental models of PD [50], and in a mouse model, it could recently be demonstrated that the loss of midbrain dopaminergic neurons leads to impairments of the circadian control of rest-activity rhythms [51].

While the interactions between SCN and melatonin-producing pineal gland are well clarified, the link between SCN and the proposed brainstem nuclei involved in

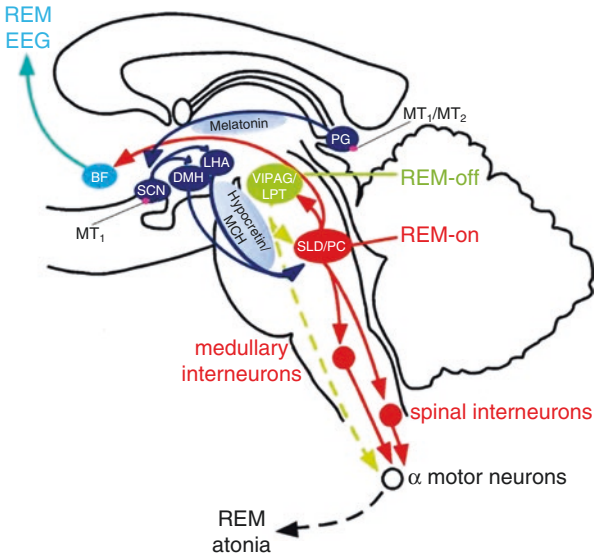

Fig. 24.1 Melatonin, circadian timing system and REM sleep in humans. Melatonin release follows a circadian rhythm and is controlled by the SCN, mainly via the MT_1 receptor, with highest levels during night, transducing the information "darkness" as a feedback signal to the SCN (blue) [2, 3]. A proposed link between circadian timing system and REM sleep controlling nuclei of the brainstem (SLD, PC) is projections of the SCN via DMH and LHA (blue) [53, 54], where MCH and hypocretin-expressing neurons participate in the regulation of neuronal activity of REM sleep [56, 57]. During REM, glutamatergic neurons in the SLD (red) activate a series of inhibitory interneurons in the medulla and spinal cord, which inhibit motor neurons, thus producing the atonia of REM sleep. Withdrawal of tonic excitatory input from the REM-off regions vlPAG/LPT (yellow, dashed lines) may also contribute to the loss of muscle tone. At the same time, ascending projections from glutamatergic neurons in the SLD and PC activate forebrain pathways (aqua) that drive electroencephalographic (EEG) desynchronization and hippocampal theta rhythms, thus producing the characteristic EEG signs of REM sleep (modified from [54]). Abbreviations: *BF* basal forebrain, *DMH/LHA* dorsomedial/lateral hypothalamic area, *EEG REM* electroencephalographic signs of REM sleep, *LPT* lateral pontine tegmentum, *MCH* melanin-concentrating hormone, *PC* pre-locus coeruleus (or subcoeruleus) area, *MT_1/MT_2* MT_1/MT_2 receptor, *PG* pineal gland, *SCN* suprachiasmatic nucleus, *SLD* sublaterodorsal tegmental nucleus, *vlPAG* ventrolateral periaqueductal gray

REM sleep control is still fragmentary. It has been shown in the rat that activity of the dorsomedial SCN (as determined by expression of PER1 gene) is associated with REM sleep propensity. This suggests that the SCN, next to gating the occurrence of sleep and wakefulness, can also shape sleep architecture by influencing the circadian sequence of specific sleep stages [52]. The SCN sends the main part of its output into the subparaventricular zone which in turn projects to the dorsomedial and lateral nucleus of the hypothalamus where MCH (melanin-concentrating hormone)-expressing neurons are active during sleep [53, 54]. Animal and in vitro studies show that acute activation of MCH neurons at the onset of REM sleep extended the duration of REM, possibly through inhibition of arousal circuits in the mammalian brain [55]. Further animal data suggest as another possible mode of action that the SCN communicates circadian phase to hypocretin-producing

cells of the dorsomedial/lateral hypothalamus via lateralized neural projections [56] whereas hypocretinergic neurons intermingled with MCHergic, and another unidentified companion group of neurons of the posterolateral hypothalamus participate in the regulation of neuronal activity in the nucleus pontis oralis, the executive site that is responsible for the generation of REM sleep in the cat [57] (summarized presentation see below in Fig. 24.1). Further research is required to gain a better insight.

Conclusions

Based on the state of knowledge, the experts of the Committee of the Standards of Practice Committee of the American Academy of Sleep Medicine (AASM) [58] suggested both clonazepam and melatonin as Level B treatments of RBD, although to date far more cases of clonazepam therapy of RBD have been reported compared to melatonin therapy of RBD. Other drugs were rated lower, given very limited evidence. Melatonin, compared to clonazepam, has the advantage of a favorable side effect profile, whereas clonazepam should be used with caution in patients with dementia, gait disorders, or OSA.

The mode of action of melatonin and melatonergic agonists in RBD still remains unclear. We hypothesize that restoration of the circadian timing system integrity, which mainly via the MT_1 receptor subsequently promotes a stronger, proper functioning of REM sleep (and proper functioning implies flawless muscle atonia), plays an important role, although confirmation of this hypothesis awaits a substantial amount of future research. The possibly different mode of action and effectiveness of short-released and prolonged-released melatonin as well as melatonergic agonists are still an open issue.

Time of administration of melatonin and its receptor agonists seems to be important. To be most effective, melatonin should be taken shortly before the usual bedtime, at the time of increasing endogenous melatonin levels, which is between 9 and 11 p.m. in intermediate chronotypes. But even more important, it should be taken about the same time every day. Melatonergic agonists may be considered for treatment of RBD, but evidence is still limited with only a few subjects having been studied [59].

Melatonin has been reported to partially restore muscle atonia during REM sleep and was shown in our studies to have a long-lasting positive effect on both clinical symptoms and PSG findings, even after melatonin discontinuation [1, 22, 23, 43]. Adequate clinical trials with a sufficient number of cases are necessary to create evidence for a safe, effective, and reliable pharmacological treatment of RBD. A consensus statement of the International RBD Study Group [60] identified essential methodologic components for future randomized trials in RBD. The committee recommended active treatment trials of melatonin versus clonazepam for assessing comparative efficacy and side effects, considering placebo-controlled studies in RBD unethical due to the risk of major, life-threatening injuries for placebo-treated patients. Potential primary and secondary outcomes for eventual trials with disease-modifying and neuroprotective agents were also defined, considering the high conversion rate from iRBD to neurodegenerative disorders. Whereas conversion rate to synucleinopathy in clonazepam-treated RBD patients

is high [61, 62], no comparable data are available yet for melatonin-treated RBD patients. In our opinion, the conversion rate in RBD patients, comparing clonazepam with melatonin, will be a most fascinating aspect of proposed upcoming trials, with proper randomization being critical. Early recognition of RBD and its effective treatment may lengthen the symptom-free period in the early phase of developing neurodegenerative disorders [63, 64].

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Clonazepam and Other Therapies of RBD

25

Carlos H. Schenck and Michael J. Howell

25.1 Introduction

RBD treatment should initially focus on controlling any sleep comorbidities (e.g., obstructive sleep apnea [OSA]), minimizing any offending medication, and maximizing the safety of the sleeping environment, as discussed by Howell in Chap. 23. The Standards of Practice Committee of the American Academy of Sleep Medicine has published a "best practice guide" for the treatment of RBD [1]. The quality and quantity of the published evidence were reviewed, and the Level A recommendation was to modify the sleep environment for patients with RBD who have sleep-related injury or in our opinion have the potential for sleep-related injury. Clonazepam and melatonin were the co-first-line medications in the Level B recommendation. Interestingly, in addition to human studies, clonazepam and melatonin were both demonstrated to be effective therapies in a transgenic mice model with deficient glycine and GABA transmission that recapitulated the cardinal features of RBD [2]. More than ten other medications were in the Level C list of alternative therapies. The worldwide clinical experience and the published evidence indicate that clonazepam and melatonin are clearly the predominant and most effective, sustained therapies of RBD. Melatonin therapy of RBD is discussed in Chap. 24. We will now focus on clonazepam therapy of RBD, followed by a review of Level C alternative pharmacotherapies and non-pharmacologic therapies. Table 25.1 contains the list of therapies for RBD.

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Table 25.1 Therapies of idiopathic and symptomatic RBD

Level A[a] secure the safety of the bedside environment
Level B[a] pharmacotherapy:
1. Clonazepam
2. Melatonin
Level C[a,b] pharmacotherapy:
3. Levodopa
4. Pramipexole
5. Rotigotine (transdermal patch)
6. Donepezil
7. Rivastigmine
8. Sodium oxybate
9. Clonidine
10. Desipramine
11. Imipramine
12. Paroxetine
13. Monoamine oxidase inhibitors
14. Carbamazepine
15. Zopiclone
16. Temazepam
17. Gabapentin
18. Cannabidiol
19. Yi-Gan San
Non-pharmacologic therapies:
1. Bed alarm
2. Immunosuppressive therapy (in CNS autoimmune diseases/paraneoplastic disorders)
3. Pallidotomy (in Parkinson's disease)
4. Bilateral subthalamic deep brain stimulation (in Parkinson's disease)

[a]From: Aurora RN, Zak RS, Maganti RK, et al.; Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med 2010;6(1):85–95

[b]Not all the medications listed in Level C were included in the above citation

25.2 Clonazepam therapy of RBD

Clonazepam, a potent benzodiazepine, was found to be effective in our index series of RBD patients at the Minnesota Regional Sleep Disorders Center [3, 4]. Clonazepam was chosen because many of the patients also had frequent periodic limb movements (PLMs) of NREM sleep, a polysomnographic (PSG) finding called "nocturnal myoclonus" in the 1980s. Case reports and case series in those years indicated that bedtime clonazepam was effective in controlling symptomatic "nocturnal myoclonus." After our initial REM-suppressing treatment strategy of RBD (with tricyclic antidepressants) failed due to intolerance, bedtime clonazepam

therapy was initiated, given its reported success with another motor disorder of sleep, viz., "nocturnal myoclonus" (PLMs) that also affected our RBD patients. We found that clonazepam not only rapidly controlled the problematic behaviors of RBD but also suppressed the disturbed dreaming (often involving aggressive confrontations) that is another hallmark of RBD. This linked benefit suggested a common pathophysiology for generating the disturbed dreaming and abnormal behaviors of RBD, consistent with involvement of brainstem motor pattern generators as encompassed by the "activation-synthesis" model of dream generation proposed by Hobson and McCarley [5].

The long half-life of clonazepam provides a greater degree of assurance to physicians and patients that it will still be bioactive during 8 h of sleep. This is of relevance as REM sleep, and thus the behaviors of RBD, predominates in the second half of the night. Conazepam does not suppress REM sleep motor tone but instead prevents the emergence of dream enactment behavior, through uncertain mechanisms.

Early large case series totaling >250 RBD patients reported a beneficial response rate to clonazepam therapy of up to 90% [6]. The world literature on clonazepam therapy of RBD, reported as small-to-large case series, now totals >500 cases, with >66% efficacy for full control of problematic RBD behaviors. The typical dose range is 0.25–1.0 mg at bedtime, ranging up to 2+ mg in select cases. Clonazepam is rarely associated with dosage tolerance (habituation effect), despite years of nightly therapy [7]. In the just-cited study, in 49 RBD patients receiving nightly clonazepam therapy for a mean 3.7 ± (SD) 2.3 years, there was no significant increase from the initial dose to the dose at the latest follow-up, 0.63 ± 0.4 mg vs. 0.97 ± 0.89 mg [7]. Also, side effects from clonazepam were uncommon (<10% of cases: morning sedation, memory dysfunction, alopecia, gastroesophageal reflux, erectile dysfunction, depression, and personality changes [emerging at the outset of therapy]), and there was no instance of misuse. As noted above, there is no published evidence that clonazepam restores normal REM atonia, and although there was initial preliminary evidence that it may reduce some of the excessive phasic EMG activity in REM sleep [8], a recent study did not confirm this finding [9].

The primary mechanism of action appears to be the control of the major, clinically problematic behaviors of RBD, without suppression of minor motor movements. This underscores the general clinical axiom that treatment should be focused primarily on the patient's chief complaint, which for RBD consists of controlling the injurious or potentially injurious behaviors, and not the minor movements. Nor is the restoration of REM atonia a necessary goal of treatment. The literature is devoid of any double-blind, placebo-controlled, randomized trials of clonazepam therapy of RBD [10–12]. However, given the recurrent injuries usually associated with RBD (with major morbidity and potential lethality [6, 13–15]), it is doubtful that an ethical treatment trial can be devised with the approval of an institutional review board. If such a trial could be devised and conducted in cases of milder RBD, i.e., not associated with violent behaviors, then the findings would not necessarily be considered generalizable to the more aggressive and violent cases of RBD.

Before initiating clonazepam therapy, any comorbid OSA should be either ruled out or else diagnosed and effectively controlled, and any offending medication (e.g. antidepressant) should be minimized or eliminated if appropriate to do so. Patients should be informed of possible side effects, as described above (along with dizziness and unsteadiness [16]). The treating physician should also be mindful of any emergent OSA triggered by clonazepam therapy of RBD [17]. Combined clonazepam-melatonin therapy can be effective in controlling RBD in patients who do not respond to either medication individually [16, 18, 19]. Furthermore, combination therapy can help facilitate lower doses of clonazepam that may minimize side effects.

Three recent studies on diverse aspects of clonazepam therapy of RBD will now be reviewed [9, 20, 21]. The first two studies were from the same center and assessed the long-term use of clonazepam in idiopathic RBD (iRBD) on REM and NREM sleep parameters and clinical treatment efficacy [9, 20]. In the first study of 57 consecutive iRBD patients (mean age, 69 years; 91% male), 42 iRBD patients not taking clonazepam (nor any other medicine) for RBD were compared with 15 iRBD patients taking clonazepam (0.5–1.0 mg) at bedtime [9]. The clonazepam-treated group had significantly lower amounts of sleep stage shifts, lower stage N1 sleep, lower % of wakefulness after sleep onset (WASO), and a higher sleep efficiency and stage N2 sleep%. None of the REM sleep parameters differed between the groups, including REM atonia index and number of REM phasic chin EMG activations. A subgroup of 13/15 clonazepam-treated iRBD patients was followed longitudinally, with vPSG parameters at a mean 2.5 year follow-up compared to the baseline parameters. These results again showed that clonazepam did not modify muscle tone during REM sleep in RBD. However, the CGI-S (clinical global impression-severity) scale scores improved with treatment. The conclusion was that clonazepam suppresses the major, clinically relevant, behavioral events in RBD and that this benefit may be related to the modification in dream content (which has been noted in numerous reports, beginning with the first formal reports on RBD [3, 4]).

The second study compared 15 patients with iRBD, 13 patients with narcolepsy-RBD, and 18 controls [20]. An additional measure that was quantified by automated analysis was NREM sleep instability. Patients with iRBD were reevaluated after a mean 2.8 years of nightly therapy with 0.5–1.0 mg clonazepam, which found increases in stages N2 and N3 sleep, a decrease in WASO, decreases in stages N1 and N2 sleep instability, and a decrease in the duration of EEG transient cortical arousals. The REM atonia index, a measure of REM sleep muscle tone, was not improved with clonazepam therapy of iRBD. However, the atonia index was increased during NREM sleep in the iRBD group compared to the other two groups, a new and interesting finding that merits further research. This study confirmed the previous study [9] that clonazepam modifies some aspects of NREM sleep (in a beneficial manner) in iRBD patients. Follow-up investigations should attempt to compare these results with findings from melatonin therapy of RBD.

The third study was a prospective, naturalistic follow-up of clonazepam treatment outcome in a series of 39 iRBD patients (mean age at diagnosis, 68 years; 74% male) [21]. Clonazepam had been offered as first-line treatment, with a mean initial

bedtime dose of 0.4 mg (range, 0.125–1.0 mg) and mean follow-up dose of 0.98 mg (range, 0.125–3.0 mg). The follow-up duration was a mean 29 months. Positive treatment response was reported to be 66.7%, using the stringent definition of "a complete elimination of sleep-related injuries and potentially injurious behaviors to self and/or bed partner." Furthermore, the frequency of disturbing dreams with violent and frightening content was also significantly reduced with clonazepam therapy. Another reassuring finding was that there was no increase in the Epworth Sleepiness Scale score after chronic clonazepam therapy of RBD compared to baseline. However, there was an increase in both level of tonic EMG activity and combined tonic/phasic EMG activity during REM sleep in the clonazepam-treated patients at follow-up compared to baseline, which confirmed a previous similar finding in iRBD patients [22]. Most likely this increased tonic/phasic EMG activity over time reflected an evolving synucleinopathy neurodegeneration in iRBD patients, which was not halted by clonazepam therapy. (A similar comparative study should be conducted for melatonin therapy of iRBD.) Finally, the authors of this study [21] modified their previously validated REM sleep behavior disorder questionnaire (RBDQ) to facilitate assessing treatment outcome in RBD, by creating a 3-month time frame for frequency of RBD events, with each item scored on a four-point scale (none; less than once per month; 1–2 times per month; ≥1 time weekly), with good internal consistency and with high correlation between the RBDQ-3M and the original RBDQ overall scale, dream-related subscale and behavioral subscale. Chapter 19 discusses the instruments used for RBD screening, the assessment of RBD severity, and monitoring treatment outcome.

25.3 Level C Pharmacotherapies of RBD

25.3.1 Dopaminergics

Levodopa, which has been used for over 50 years as the predominant therapy in Parkinson's disease (PD), has only limited efficacy in RBD. In a series of three patients with PD preceded by presumed RBD (no PSG was performed), levodopa was reportedly effective in controlling the presumed RBD [23]. However, during this earlier period, history-taking for RBD was not well established, and the lack of PSG documentation predisposed to potential large discrepancies between subjective complaints and objective findings, resulting in uncertainty in regard to the parasomnia diagnosis and the basis for improvement of motor symptoms in response to treatment. Conversely, a prospective case series in previously untreated PD patients reported the onset of RBD in less than 1 year after initiating levodopa therapy in 5/15 PD patients [24]. Clearly, levodopa therapy did not prevent the emergence of RBD in these PD patients. Of note, a systematic study of 35 PD patients found that those with RBD generally used higher doses of levodopa than those without RBD in the context of comparable disease stages [25]. This finding is consistent with other studies in PD indicating that comorbid RBD predicts a more aggressive course of disease.

Pramipexole, a dopamine receptor agonist, has been shown in four case series to be effective in 62–89% of patients with iRBD, RBD associated with mild cognitive impairment, or RBD with mild PD [26–29]. On the other hand, a prospective study of patients with combined RBD-PD found no benefit in reducing the severity or frequency of RBD when pramipexole was added to a stable levodopa regimen [30]. The starting dose of pramipexole in the therapy of RBD should be 0.125 mg at bedtime, with gradual increments by 0.125 mg, up to a maximum of 2–4 mg at bedtime.

Pramipexole appears to be most effective in RBD cases associated with frequent PLMs (in both NREM and REM sleep). PLMs in NREM sleep are a common PSG finding in RBD and are often responsive to dopaminergics. One investigation noted that compared to clonazepam-responsive RBD patients, pramipexole-responsive RBD patients had more mild disease at baseline as measured by the level of REM sleep atonia [28]. Similar to treating OSA in RBD (see Chap. 23), pramipexole may decrease nocturnal symptoms by reversing a sleep-fragmenting condition, viz., PLMs. Another pramipexole study in RBD patients reported a decrease in distressing nocturnal behaviors along with a decrease in PLMs, but no effect on REM sleep atonia [29]. Pramipexole therapy of RBD has recently been critically reviewed [31].

Rotigotine, a dopamine agonist of the non-ergoline class, has recently been shown to be partly effective in treating RBD symptoms in the setting of PD [32]. In a prospective open-label study, 11 PD patients with untreated RBD received rotigotine transdermal patches for up to 7 months as therapy of their PD. Severity of RBD symptoms before and after rotigotine therapy was evaluated by patient and bed partner interviews, a validated scale (RBDQ-HK, described above and in Chap. 19), and blinded assessments based on vPSG measures. Rotigotine improved PD and subjective sleep quality in the PD-RBD patients. Subjectively, RBD symptoms were improved, particularly the frequency and severity of abnormal RBD behaviors. However, objectively, the vPSG analyses found no differences in RBD-related sleep measures (a common theme with the pharmacotherapy of RBD).

25.3.2 Other Agents

These initial findings encourage the further study of dopaminergics in RBD, and suggest that these agents could be considered as RBD treatment options, especially in the setting of elevated PLMs among RBD patients with PD. The mixed therapeutic results with dopaminergic therapy of RBD may seem perplexing, given the strong link between RBD and PD/other synucleinopathies, and the eventual >80% phenoconversion from iRBD to a parkinsonism disorder (as described in Chaps. 4–6). Why shouldn't dopaminergic therapy be the first-line therapy of RBD? The negative answer to this logical question illustrates the complex neurochemistry, neuroanatomy, and neurophysiology subserving REM atonia and the phasic REM sleep motor-behavioral system. This is addressed in the basic science section (Chaps. 39, 42, 43). There is also a novel animal model of RBD (with clinical

implications) produced by genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus [33, 34].

Acetylcholinesterase inhibitors (AIs), which can trigger RBD in Alzheimer's disease [35, 36], have been reported as effective therapy of iRBD. Donepezil, in doses of 10–20 mg, was beneficial in two reports involving one case series of ten iRBD patients, with vPSG performed in 9/10 patients (although a 29-year-old man by description most likely had a NREM parasomnia along with RWA) [37, 38]; rivastigmine, in doses up to 6 mg at bedtime, was also reported to be effective in this series. Rivastigmine efficacy has also been reported in treatment-resistant, PSG-confirmed, RBD with PD, and in treatment-resistant, PSG-confirmed, RBD with mild cognitive impairment (MCI) [39, 40]. In these cases, the enhancement of central cholinergic neurotransmission with AI therapy was proposed to be the mechanism for the control of RBD not associated with dementia. However, donepezil therapy was not effective in controlling RBD severity or frequency in patients with neurodegenerative disorders [18]. Thus, AI therapy of RBD should be considered third-line therapy or else may be used as first-line therapy in symptomatic RBD associated with MCI, PD dementia, or dementia with Lewy bodies.

Sodium oxybate, an effective anti-cataplectic agent, has been reported to be effective monotherapy or supplemental therapy of RBD in six carefully described cases ($n = 5$, prior treatment-resistant cases; $n = 1$, *de novo* treated case) that will now be presented to allow a "first-hand feel" for the eventual successful management of treatment-resistant RBD cases. The first case was reported by Shneerson in 2009, involving a 66-year-old married man with a 2.5 year history of injurious dream-enacting behaviors documented to be caused by RBD with video-PSG (vPSG), in which he made running movements, aggressive arm gestures, shouting, and leaping from bed during REM sleep [41]. There was no neurological disorder, and so he was diagnosed with iRBD. After failing treatment with clonazepam, temazepam, zopiclone, melatonin, gabapentin, and clonidine, treatment with *sodium oxybate* was started, with control of RBD behaviors and nightmares within 4–5 days. This benefit was maintained, without further injury, at 1-year follow-up, at a dose of 4.5 gm at bedtime, without any side effects. The second case involved a man whose RBD persisted with nightly nightmares, screaming, and occasional injuries despite taking clonazepam 4 mg/night, melatonin 12 mg/night, and quetiapine 100 mg/night. However, with the addition of sodium oxybate at 3 g twice nightly, his RBD was almost completely controlled [19]. Sodium oxybate monotherapy was eventually achieved, with full ongoing control of the RBD. However, if he failed to take the sodium oxybate, RBD would invariably recur.

A third case involved a man in his late 60s with a 15-year history of PD and 20-year history of violent RBD episodes occurring 3–4 nights weekly, with recurrent injuries to himself and his wife [42]. Deep brain stimulation therapy of PD improved daytime motor PD symptoms, but the RBD worsened, with nightly aggressive episodes. After vPSG confirmation of RBD (and mild OSA; AHI = 8.5), sequential therapy with clonazepam (1 mg), melatonin (12 mg), prazosin, ramelteon, cyproheptadine, and eszopiclone was ineffective, and violent RBD episodes increased in frequency and severity. Sodium oxybate therapy was started, with the dose titrated to 2.5 g twice nightly. There was rapid and complete RBD symptom

resolution for 2 months, and then because of rare subsequent breakthrough episodes, the dose was increased to 3 g twice nightly, with complete control of RBD at 1.5 year follow-up. There were no reported side effects. Repeat vPSG on sodium oxybate therapy revealed the persistence of REM without atonia (RWA), without any dream-enacting behavior, and the AHI = 12.8.

Two other reported cases of iRBD treated with sodium oxybate involved 68- and 51-year-old males [43]. In the first case, there was a 10-year history of RBD, with multiple nightly dream-enacting episodes with beating and choking the bed partner, and sustaining injuries (e.g., fracturing his arm). vPSG confirmed RBD, but bedtime therapy with clonazepam (2 mg), alone or combined with carbamazepine (400 mg) and lamotrigine (25 mg), was inadequate and/or poorly tolerated. There was a temporary response to pramipexole (up to 0.45 mg) and melatonin (5 mg). Medical history was negative. Neurologic exam revealed fatigue and mild hyposmia. Sodium oxybate was started, with the dose titrated to 4.5 g twice nightly, with pramipexole 0.45 mg and melatonin 5 mg continued. The patient eventually reduced the dose to 4.5 g at bedtime. There was dramatic improvement of RBD noted by the patient and bed partner within the first weeks of therapy. Repeat vPSG revealed the persistence of RWA. Melatonin was withdrawn without worsening of RBD. However, pramipexole withdrawal resulted in clinical worsening of nocturnal behaviors, and so it was restarted. Actigraphy showed sustained resolution at 4-year follow-up. Benefit of combined sodium oxybate (4.5 g at bedtime) and pramipexole (0.45 mg at bedtime) was continued at 5.5-year follow-up, as confirmed by the patient and his wife. The only side effect reported was mild constipation.

In the second case, there was an 8-year history of RBD, with episodes occurring up to twice weekly with multiple injuries, including a fracture of one of his nasal bones, hitting and choking his wife during dream enactment of chasing thieves, and fighting. vPSG confirmed RBD, without sleep-disordered breathing. There was a temporary response to clonazepam, 2 mg alone, then together with melatonin 5 mg, and finally with pramipexole up to 0.36 mg, but in each case, he soon became refractory. Sodium oxybate, 1.5 g twice nightly, was added to clonazepam 2 mg at bedtime. There was dramatic improvement noted within first month with a decrease in frequency and intensity of the episodes. The bed partner confirmed the cessation of complex and violent episodes. Sporadic minor movements and sleep talking persisted. Repeat vPSG showed the persistence of RWA. An attempt at clonazepam withdrawal resulted in RBD relapse, and so he was maintained on 2 mg clonazepam at bedtime together with sodium oxybate 1.5 g twice nightly, with benefit maintained at 2.5-year follow-up. Mild morning sleep inertia was the only reported side effect. Neurologic exam did not detect any parkinsonism. The sixth reported case of sodium oxybate efficacy (as initial therapy) in RBD with violent, injurious dream-enacting behaviors, involved a 56-year-old male patient with comorbid narcolepsy type 1 [44]. Future systematic research on sodium oxybate therapy of RBD should include cohorts of patients with narcolepsy-cataplexy-RBD, and not just treatment-resistant iRBD or other types of symptomatic RBD. The mechanism(s) of action of sodium oxybate in the control of treatment-resistant cases of iRBD and PD-RBD, and in narcolepsy type 1-RBD remains to be elucidated.

Further support for the use of SO as effective therapy of RBD was found in a recent study on the effect of chin muscle tone during sleep with SO therapy of narcolepsy type 1 [45]. The analyses included short (<0.5 s) and long (>0.5 s) chin muscle activity indices per hour. A validated semiautomatic analysis of muscle tone was utilized. A total of 116 patients were studied, with PSG performed at baseline, 4 weeks after titration of SO to 4.5, 6, 9 g, or placebo, and after another 4 weeks on a stable SO dose. A major finding was that long (>0.5 s) chin muscle activity decreased significantly during REM sleep, especially with high doses of SO, thus encouraging its therapeutic use in RBD, particularly in RBD comorbid with narcolepsy type 1, and also in RBD treatment-resistant cases.

However, side effects from SO should be anticipated in some cases, including sexsomnia [46] and sleep-related eating disorder (SRED) [46], as reported in a case of a 41-year-old woman with narcolepsy type 1, whose therapy with SO induced the onset and recurrence of these two parasomnias, in which she would sexually assault her husband (at times culminating in full intercourse) while talking obscenely, and she would also go to the kitchen to eat "voraciously" (including immediately after having sex), for which she always had subsequent amnesia [47]. These parasomnias promptly resolved upon discontinuation of SO. (Sexsomnia and SRED are discussed in Chap. 27 on Parasomnia Overlap Disorder.)

Other therapies of iRBD or symptomatic RBD (apart from melatonin and melatonin receptor agonists that are discussed in Chap. 24) described in case reports and small case series reported to be effective include clonidine (a potent suppressor of REM sleep) [48], desipramine/imipramine [6, 49] (i.e. TCAs that can also trigger or aggravate RBD), paroxetine [50, 51], monoamine oxidase inhibitors [52], carbamazepine [53], zopiclone [54], temazepam [54], gabapentin [55], and cannabidiol [56]. The finding that paroxetine, an SSRI that can trigger or aggravate RWA/RBD in Caucasians [57]—along with fluoxetine [58], sertraline [59], and other SSRIs—was effective in controlling RBD in Japanese patients [50, 51] raises questions about ethnically mediated, divergent pharmacologic responses in RBD.

Yi-Gan San, an herbal preparation whose prescription is approved in Japan for treating insomnia, contains seven herbal ingredients, including Angelicae radix that has been reported to affect 5-HT2 and GABA receptors. Three cases of PSG-confirmed RBD from Japan have been reported in which the RBD (in a 60-year-old man and 74- and 87-year-old women) with aggressive dream enactment responded to Yi-Gan San therapy, taken at a dose of 2.5 gm ($n = 1$) or 7.5 gm ($n = 2$), with one patient also taking low-dose clonazepam (0.25 mg) [60].

25.4 Non-pharmacologic Therapies of RBD

Bed Alarm [61]. Exiting the bed while acting out a dream is a particularly high-risk behavior and may result in severe traumatic injury. Intriguingly, the low arousal threshold and rapid transition to alert wakefulness from REM sleep offers a therapeutic window to halt exiting the bed prior to sleep-related injury with RBD. Despite

apparent unconsciousness during REM sleep, the brain is readily responsive to complex auditory sound processing. This contrasts with the high arousal threshold of NREM sleep often demonstrated by the inability to redirect or wake up sleepwalkers (a NREM parasomnia). A study of patients with medication refractory RBD and sleep-related injury demonstrated the utility of a customized bed alarm that delivered a calming message at the onset of dream enactment behavior [61]. Ideal voices, typically those of family members, were identified, and commands to halt dream enactment behavior were then recorded (e.g., "Dave, you are having a dream, lay back down"). Subsequently, when the patient arose during sleep, the voice emanated from a bedside speaker on a repeating loop until the patient returned to lying down on the pressure pad.

Immunosuppressive therapy of RBD in cases associated with CNS autoimmune diseases and paraneoplastic disorders will be discussed by Iranzo in Chap. 8.

Pallidotomy was effective in one case of RBD associated with Parkinson's disease (PD) [62]. Whereas chronic bilateral subthalamic deep brain stimulation (DBS) was not effective for RBD in two reports [63, 64], in a recent report of three PD patients with RBD associated with parasomnia overlap disorder (POD: RBD + NREM sleep parasomnia, covered in Chap. 27), with these patients undergoing bilateral subthalamic DBS, one of the patients, a 70-year-old woman, demonstrated an impressive therapeutic response [65]. Episodes of dream enactment and confusional arousals were suppressed, sleep talking became rare, and sleep architecture markedly improved after DBS treatment. Also, comparing the PSG findings before vs. after DBS treatment, there was a 44% reduction in REM sleep chin tonic muscle activity and 8% reduction in REM sleep phasic muscle activity. In contrast, the other two RBD/POD patients in this DBS treatment group (males, 55 and 75 years old) had deterioration of their RBD/POD posttreatment. Interestingly, an isolated episode of RBD has been reported immediately following left subthalamic electrode implantation for the treatment of Parkinson's disease [66].

Finally, successful control of RBD with appropriate pharmacotherapy, or other somatic therapy, also usually controls the "environmental sleep disorder" [46] for the bed partner (i.e., wife) that had involved long-standing, recurrent sleep disruption and injuries from the RBD. This demonstrates how effective therapy of one person's sleep disorder, viz., RBD, can restore normal, uneventful, and restful sleep in the bed partner.

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Differential Diagnosis and Related Disorders: RBD Mimics

26

Raffaele Manni and Michele Terzaghi

26.1 Introduction

REM sleep behavior disorder (RBD) presents as motor-behavioral, acting-out-a-dream-type episodes during REM sleep, with motor-behavioral manifestations varying widely. Jerky movements, vocalizations/talking/shouting, as well as dream mentation reports are hallmarks of RBD. However, quite a few other nocturnal conditions of different origin have features that are similar or are reportedly similar to those of RBD. The likeness is particularly striking in other parasomnias, sleep-related movement disorders, and other abnormal events during sleep, which may be considered true RBD mimics. Moreover, RBD and its mimics may co-occur within the same symptomatic context, in acute diseases (as in the case of RBD associated with acute-onset structural, vascular, demyelinating, tumor-associated brain lesions and with other diseases such as encephalitis and Guillain-Barré syndrome, drug intoxication or alcohol withdrawal, and acute post-traumatic stress disorder) [1] as well as in chronic diseases, namely, synucleinopathy neurodegenerative disorders. This may further complicate distinguishing the disorders from one another on the grounds of the clinical reports and even video findings. Several questionnaires and scales [2, 3] as well as video analysis-based algorithms have been developed to appropriately screen for probable RBD, with the rate of false-negative and false-positive cases varying according to the clinical context and the more-or-less critical use of these tools.

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The recent literature [4] has shown that the RBD screening questionnaire value in correctly identifying RBD in PD strongly depends on the clinical setting. The same questionnaire was reported not to predict REM without atonia (RWA) [5] which is the essential polysomnographic feature to diagnose RBD in cryptogenic (idiopathic) as well as in forms of RBD associated with PD. In fact, a definite diagnosis cannot be reached with the lack of confirmatory overnight video-polysomnography (vPSG), which may however not give unequivocal findings in some particular, complex contexts.

The various potential mimics of RBD will be reviewed and discussed in light of the clinical and V-PSG distinguishing features with respect to RBD.

26.2 Parasomnias

26.2.1 Disorders of Arousal

26.2.1.1 NREM Arousal-Related Parasomnias (Sleepwalking, Sleep Terrors, Confusional Arousals)

Disorders of arousal (DOA) are NREM-related disorders that result from incomplete arousals from slow wave sleep. DOA cover a wide range of nocturnal anomalous episodes, essentially characterized by emotional behaviors and motor output of various complexities and durations, vegetative activation of different degrees, misperception of the environment and relative unresponsiveness to external stimuli, mental confusion, automatic behaviors, and variable retrograde amnesia.

Confusional arousals, sleep terrors, and sleepwalking can generate by history difficulties in distinguishing from RBD, when they have their onset or relapse in adulthood. Indeed, an estimated prevalence rate of 1.5% (95% CI 1.0–2.3%) for sleepwalking [6], 2–4% for sleep terrors, and 2.9–4.8% for confusional arousals was reported in adults [7, 8]. The timing of occurrence of the episodes during the first part of the night and the lack of clear recall of dream mentation are considered peculiar to DOA and typical distinguishing features from RBD. However DOA may arise, although infrequently, during the second part of the night [9] and may be associated with unfavorable dream mentation (mainly the recollection of negative dreams with misfortune) of variable complexity and duration, albeit presumably different from RBD [10, 11].

In fact, studies of dreamlike mentation during DOA as opposed to RBD showed the existence of different patterns in the two disorders potentially reflecting physiological dreaming differences in NREM and REM sleep: enacted behaviors observed in DOA represent fleeing a disaster while during RBD counterattacking a human or animal assault [10, 11] (Chap. 17 discusses dreaming in RBD).

The occurrence of walking out of bed or out of the bedroom and running is a feature of sleepwalking. In contrast, ambulation is rarely reported in RBD. However, episodes of leaving the bed and ambulation were reported to occasionally occur in 24% of the subjects in a series of 204 iRBD patients [12]. Furthermore, a comorbidity of RBD and SW was reported in PD, with this finding leading the authors to

hypothesize that a common underlying dysfunction of motor control during sleep may exist in PD patients [13].

Confusional behaviors characterized by confabulation, sitting up in bed or getting up, and wandering around the room or outside it, with the inability to give correct answers to the bed partner and partial or complete amnesia the following morning, are suggestive of confusional arousals [14]. These episodes may turn out to be hard to distinguish from RBD without video-PSG, namely, forms of RBD with nonviolent, elaborate behaviors [15].

26.2.2 Pseudo-RBD in OSA

A case series of subjects with obstructive sleep apnea (OSA) presenting with dream-enacting behaviors suggestive of RBD was reported by Iranzo et al. [16] in a seminal work which alerted clinicians about the potential misdiagnosis of RBD in OSA. Complex motor-behavioral events were found to occur upon arousals from obstructive apnea/hypopneas in patients with severe forms of OSA (AHI ranging from 41 to 105), and this condition was named "OSA pseudo-RBD." The subjects were found to have preserved REM sleep atonia, with the RBD-like episodes concomitant to apnea-/hypopnea-induced arousals arising from NREM and REM sleep. Treatment with continuous positive airway pressure (CPAP) proved to eliminate the abnormal behaviors and unpleasant dreams together with snoring and daytime hypersomnolence, and follow-up V-PSG studies confirmed the efficacy of CPAP and reconfirmed the preservation of REM atonia. Recently, a case report further confirmed that dream-enacting behaviors suggesting the diagnosis of RBD can occur only during respiratory event-induced arousals in severe obstructive sleep apnea, and that continuous positive airway pressure restores a normal sleep [17].

While potentially misleading in themselves, pseudo-RBD episodes may co-occur with true RBD in a given patient, with the RBD and OSA comorbidity making it particularly difficult to distinguish one type of episode from the other.

26.2.3 Nightmares

Nightmares involve a perturbation of emotional expression during sleep. In the form of recurrent dreams, the disorder is characterized by unpleasant vivid dream mentation permeating REM sleep: being threatened, being imprisoned, and fighting overwhelming natural forces [18, 19]. Nightmares typically become more and more disturbing as they unfold. Resembling RBD, the episodes occur during the second half of the night, can be characterized by negative emotions such as fear or anger from imminent physical danger, and may occur as multiple events within a single sleep episode. The ability to detail the nightmare's contents without confusion on nighttime awakening, along lack of motor-behavioral outputs, is typically considered a distinguishing feature of nightmares with respect to RBD. However, the differential diagnosis of nightmares with respect to RBD may turn to be difficult. For example, this can occur in nightmares emerging with PTSD [20], in the so-called to trauma-associated

sleep disorder (TSD), where the co-occurrence of nightmares, and associated RBD-like behaviors, together with PSG findings of mild-to-moderate REM without atonia, constitutes a complex clinical PSG entity that challenges the diagnostic process [21].

26.2.4 Sleep Talking

Sleep talking is a very common phenomenon in the general population [22]. Talking is associated with various degrees of comprehensibility, and sleep talkers can engage in complex conversations and even answer correctly to other speakers, but are rarely aware of their sleep talking, with little or no recall on the next morning. Sleep talking content is various, is not associated to enactment of a dream, and can occur during NREM and REM sleep without a particular timing in the night [23]. As sleep talking is part of RBD manifestations and was reportedly [24] a frequent phenomenon in the RBD patients' past history, it should be included in the differential diagnosis with respect to RBD.

Sleep talking, especially when loud and aggressive, or when other vocalizations occur, such as singing and screaming, should drive attention to seek out other sleep alterations suggestive of RBD. This is particularly recommended in the context of neurodegenerative disorders associated with dementia and RBD (i.e., DLB, PDD) [25].

26.3 Psychogenic Disorders

26.3.1 Nocturnal Dissociative Disorders

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-V) lists a sleep-related variant of dissociative disorders. This includes dissociative identity disorder and dissociative fugue that occur during nocturnal wakefulness. Psychological testing together with a past, generally childhood, history of (usually sexual) abuse may facilitate distinguishing sleep-related dissociative disorders from RBD. V-PSG can help in difficult clinical cases, and in cases with forensic implications, demonstrating that "sleep-related dissociative" episodes, at times with agitated behaviors, actually occur in a clear pattern of EEG wakefulness after an awakening from light NREM sleep (and not from deep NREM sleep that occurs with NREM arousal parasomnias) [26].

26.4 Sleep-Related Movement Disorders

26.4.1 Rhythmic Movement Disorder

Rhythmic movement disorder (RMD) features rhythmic rocking, rolling, or banging movements involving any part of the body during quiet wakefulness, drowsiness, or sleep. RMD is rare after the age of 4 years even though cases in adult life

have been documented. Usually, the clinical picture of rhythmic movement disorder is one of a mild, sporadic motor disorder, with mild consequences. However, more severe forms with events occurring upon consecutive nights and violent RMs resulting in self-injuries have been reported. Injuries include forehead bruises, skull and soft tissue contusions, but also, in extreme cases, subdural hematoma, hemoglobinuria, and carotid dissection [27]. V-PSG studies showed that RMs can occur during REM sleep [28], especially in adults as de novo or relapsing events.

Finally, in adults rhythmic movements may occur in the context of RBD [29, 30], indicating that in some cases the differential diagnosis between the two conditions may be difficult **solely** on **an** anamnestic basis.

26.4.2 Periodic Limb Movement Disorder (PLMD)

Periodic leg movements (PLMs) during sleep consist of stereotypic flexions/extensions of the toe, at times in combination with flexion of the ankle, the knee, and the hip. Spreading or similar movements can be observed in the upper limbs. These events can be associated with an autonomic or cortical arousal or even an awakening. When the frequency is >5/h in children or >15/h in adults and the PLMs cause clinically significant sleep disturbance, the PLMs meet the diagnosis of PLMD.

Gaig et al. [31] reported a cohort of subjects who were referred because of history dream RBD-like episodes. The episodes consisted of talking, shouting, kicking, punching, gesticulating, falling out of bed, and even assaulting the bed partner and were documented to occur during NREM sleep arousals triggered by the occurrence of PLMs involving the arms and legs. Dopaminergic treatment resulted in amelioration of PLMs and disappearance of the abnormal behaviors. This study thus supports the designation of "PLMD pseudo-RBD" that should be included in the differential diagnosis of RBD, particularly since the clinical profile in this study matches the main clinical profile in RBD, viz., older men.

26.5 Epileptic Nocturnal Seizures

Ictal and postictal phenomena of sleep-related epileptic seizures, namely, arising from temporal and frontal lobe (including the sleep-related hypermotor epilepsy [SHE]), may result in a complex differential diagnosis versus RBD [32]. In spite of tonic and dystonic postures and stereotypical motor manifestations strongly suggestive of SHE rather than RBD, nevertheless the hyperkinetic manifestations of SHE consisting of brisk, violent, arm, and/or leg movements may remind of those seen in RBD [33].

Motor and verbal automatisms during temporal lobe seizures may mimic the semi-purposeful gesturing, utterances, and sleep talking found in RBD, and abrupt movements, wandering, shouting, aggressive behaviors, or vivid dreamlike enactments may be reminiscent of the aggressive behavior seen in RBD. Despite REM sleep usually suppressing ictal and interictal epileptic phenomena [34], epileptic

seizures have been reported to occur during REM sleep. For example, a case was reported of a 16-year-old boy who was documented to have seizures on awakening from nearly every nighttime REM sleep period, with a swift falling back to REM sleep after each fit [35].

A scale (FLEP scale) is available in helping to distinguish epilepsy from NREM parasomnia and RBD [36]. However, an intrinsic limitation in the power of this scale would suggest using it as an additional tool only in association with obtaining a clinical history and instrumental evaluations [37]. But rarely, the risk of misdiagnosis is increased by the possibility of comorbidity between epileptic phenomena and RBD. Comorbidity can occur in terms of presence of interictal epileptiform abnormalities during wake and/or sleep in RBD patients or of co-occurrence of RBD and epileptic seizures in the same patient (up to 12.5% of a series of 80 elderly subjects with epilepsy) [38, 39]. Time-synchronized V-PSG with extended EEG montage is mandatory to establish the nature of a patient's motor-behavioral episodes when epilepsy is suspected [40].

26.6 Other Conditions

26.6.1 Insulinoma-Related Hypoglycemia

Insulinoma is a rare endocrine tumor causing a wide variety of symptoms [41] including abnormal nocturnal behaviors. Symptoms of hypoglycemia can mimic psychiatric, epileptic, and other neurological symptoms and sleep disorders. Three subjects with insulinoma were reported to show abnormal nocturnal behavior and injury during sleep, simulating RBD [42]. The abnormal manifestations included stereotypical behaviors (repeatedly opening and closing the bathroom door, clapping of hands and walking with sumo wrestler-style leg stomps in a circle around the fireplace) and sustaining injuries, but apparently not related to dream content, and also subsequently finding furniture or blankets out of place. In all the cases, abnormal behaviors occurred at home, and overnight in-lab PSG did not show REM sleep without atonia or complex motor behaviors during REM sleep. Improvement in nocturnal hypoglycemia resulted in disappearance of the abnormal nocturnal behaviors.

The authors recommended nocturnal and early morning glucose monitoring in atypical RBD-like cases without any loss of REM atonia.

26.6.2 Malingering

Malingering may masquerade as RBD, and it may be difficult to distinguish between cases of malingering and genuine RBD episodes. Careful clinical history and V-PSG can document the occurrence of malingering episodes while the subject is awake or, in the absence of overt clinical manifestations during the monitored night, the lack of the characteristic findings of RBD [36, 43].

26.6.3 Sleep-Related Violence Episodes

Sleep-related violence encompasses a wide variety of violent events during sleep with different etiologies that may be difficult to distinguish from one another.

Violent behaviors with injuries to self or others may occur during RBD.

All these episodes may have forensic implications [36, 43, 44], and sleep specialists may be involved in the evaluation of cases of sleep-related violence.
Guidelines for the assessment of sleep-related violence episodes have been proposed [45], which for the diagnosis of RBD is established mainly by V-PSG findings together with the clinical findings.

26.7 RBD Mimics in Special Contexts: RBD Chameleons in PD and Other Synucleinopathies

Abnormal arousal-related motor-behavioral episodes arising during NREM sleep and closely resembling RBD were described in the context of PD and DLB [46–49]. These episodes consisted of short-lasting, minor jerky movements of the limbs ranging up to complex, semi-purposeful movements and full-blown violent behavior (with kicking, punching, running).

In our cohort of extrapyramidal disease subjects, 3% of 362 consecutive subjects (affected by PD, DLB, or MSA) showed such events for a total of 30 episodes recorded. The episodes occurred invariably during NREM sleep (20%, N1; 40%, N2; and 40%, N3, respectively) and were indistinguishable from RBD episodes from a clinical point of view (Fig. 26.1). The analysis of the timing of the events during V-PSG showed that 63.3% of the events occurred close to episodes of REM sleep, while 36.7% occurred in periods of the night distant from REM sleep, with the episodes occurring either as an unique event (36.4%) or in clusters (63.6%).

The pathophysiology and the ultimate neurobiological meaning of these events remain to be elucidated. One could interpret them in the framework of the dissociated states of being theory [50]. In particular, these episodes could be seen as an expression of covert REM sleep, i.e., as episodes of NREM sleep during which REM sleep processes co-occur while REM sleep cannot be scored according to standard PSG scoring criteria [51]. The occurrence of dissociative features of NREM and REM sleep could be explained, in the particular context of synucleinopathies, by the activation of a defective arousal system, due to neurodegenerative alterations of the brainstem reticular network, which ultimately become unable to drive a complete transition across NREM and REM sleep.

A co-occurrence of NREM sleep arousal-related motor-behavioral episodes and episodes of RBD, in a clinical scenario of "parasomnia overlap disorder," occurred in some patients. It can be hypothesized that the combination of NREM episodes and RBD could represent an advanced form of motor dyscontrol during sleep caused by cortical/subcortical neurodegeneration. (Parasomnia overlap disorder is the topic of Chap. 27.)

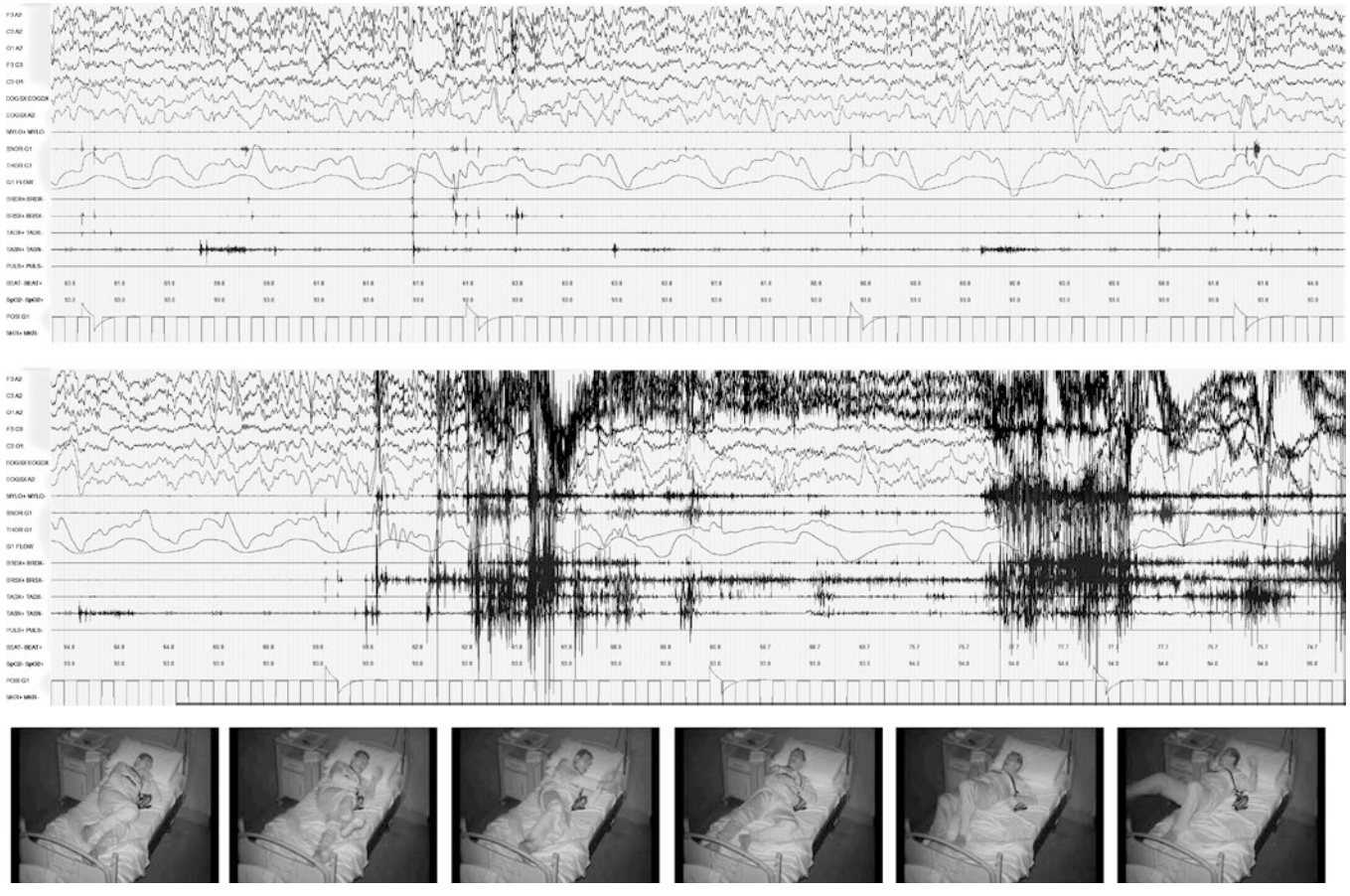

Fig. 26.1 RBD-like motor-behavioral episode arising during NREM sleep in a subject diagnosed with probable DLB

26.8 Conclusions

A correct diagnosis of RBD with exclusion of mimics is of great importance because misdiagnosis of RBD may carry noteworthy clinical and ethic consequences. As clearly shown in the literature, idiopathic RBD implies to have a critical risk of developing a neurodegenerative disorder, with median conversion time of 4–9 years from RBD diagnosis and of 11–16 years from symptom onset. Given the consensus to disclose the neurodegenerative risk to patients [52] and to include them in prospective monitoring implying time- and resource-consuming activities, a correct diagnosis has clear ethic and organizational benefits. Furthermore, a correct diagnosis of RBD is important since this parasomnia is usually treatable, and RBD subjects should be informed about the possibility of seriously injuring themselves.

In diagnosing RBD clinicians should be aware of the several potentially tricking RBD mimicking events. A few clinical parameters may be taken into account to distinguish RBD from RBD mimics. However only V-PSG can lead to a correct diagnosis. A single full-night time-synchronized video-PSG recording is usually adequate to establish a definite diagnosis of RBD [53]. Extended montages, allowing the simultaneous recording of various physiological parameters (muscle activity, respiratory pattern, extended EEG montages), should be taken into consideration when the possibility of mimics or comorbidities cannot be ruled out by clear anamnestic findings.

26.8.1 "Take-Home" Messages

1. Many motor-behavioral events may simulate or co-occur with RBD.
2. Severe obstructive sleep apnea and PLMD may release RBD-like behaviors (with dream enactment) as an epiphenomenon of a disordered arousal manifestation.
3. NREM sleep events clinically indistinguishable from RBD can occur in synucleinopathies.
4. Disorders of NREM sleep arousal, rhythmic movement disorder, temporal and frontal nocturnal epileptic seizures, severe nocturnal hypoglycemia-related episodes, and psychogenic disorders may mimic RBD.
5. Differential diagnosis can be challenging, especially in cases of comorbidity of RBD and its mimics.
6. A few clinical parameters, such as the semiology of the episodes, dream-related mentation, and timing during the sleep period, may help in distinguishing RBD from RBD mimics, but only V-PSG can help establish a definite correct diagnosis.

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Parasomnia Overlap Disorder: RBD and NREM Parasomnias

27

Carlos H. Schenck and Michael J. Howell

27.1 Introduction

Parasomnia overlap disorder (POD) was formally described and named at the Minnesota Regional Sleep Disorders Center in 1997 with a series of 33 cases of RBD combined with a disorder of arousal from NREM sleep (confusional arousals, sleepwalking [SW], sleep terrors) that emerged idiopathically or symptomatically with neurological and other disorders [1]. The presenting complaint was sleep-related injury; mean age was 34 ± (SD) 14 years, and mean age of parasomnia onset was 15 ± 16 years (range 1–66); 70% were males. An idiopathic subgroup ($n = 22$) had a significantly earlier mean age of parasomnia onset (9 ± 7 years) than a symptomatic subgroup ($n = 11$) (27 ± 23 years) ($p = 0.002$). It was usually indeterminate which parasomnia emerged first (RBD vs. NREM parasomnia), or whether they emerged concurrently. Diagnosis was determined by clinical interview and exam, followed by overnight video-polysomnography (vPSG) that documented both RBD and a NREM parasomnia. Autonomic nervous system activation (tachycardia, tachypnea, diaphoresis) during behavioral episodes predominantly occurred with a NREM parasomnia (viz., sleep terrors) rather than with RBD with vigorous dream enactment (a typical and intriguing finding in RBD). Treatment outcome was available for 20 patients, and 90% ($n = 18$) reported substantial control of their parasomnias with bedtime clonazepam ($n = 13$), alprazolam/carbamazepine ($n = 4$), or hypnosis ($n = 1$). Thus, POD was found to be a treatable condition that emerges

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Table 27.1 Classification of parasomnia overlap disorder involving RBD

1.	RBD-NREM parasomnia (sleepwalking/sleep terrors—disorders of arousal from NREM sleep):
(a)	Idiopathic
(b)	Symptomatic:
	Neurologic (Parkinson's disease; narcolepsy; multiple sclerosis; brain tumor and therapy; traumatic brain injury; Machado-Joseph disease; acute rhombencephalitis [right pontine tegmentum/medulla lesion]; congenital Möbius syndrome; anti-IgLON5 syndrome; Harlequin syndrome; Creutzfeldt-Jakob disease; indeterminate neurologic disorder)
	Psychiatric (posttraumatic stress disorder/major depression; chronic alcohol and amphetamine abuse and withdrawal; mixed disorders)
	Cardiologic (nocturnal paroxysmal atrial fibrillation)
	Mixed disorders (traumatic brain injury/chronic alcohol abuse and withdrawal; schizophrenia, antipsychotic/anticholinergic therapy, chronic alcohol and cocaine abuse)
2.	Subclinical RBD (REM-without-atonia)—NREM sleep parasomnias (idiopathic; symptomatic)
3.	RBD-sleep-related eating disorder (NREM sleep parasomnia)
4.	RBD-sexsomnia (NREM sleep parasomnia)
5.	RBD-rhythmic movement disorder (head rolling in REM Sleep)

either idiopathically or with various clinical disorders, as listed in Table 27.1 (that contains an update with the cumulative POD literature, as described below). POD was found to be common at our center, comprising more than 20% of all RBD cases and almost 30% of all NREM parasomnias cases [1]. Although POD is classified as a subtype of RBD in the International Classification of Sleep Disorders, 3rd edition (ICSD-3) [2], diagnostic criteria for both RBD and a NREM parasomnia must be met in order to diagnose POD [2].

A literature review in our 1997 publication also identified two prior cases of POD [1]: (1) a 51-year-old man with Machado-Joseph disease (spinal-cerebellar-ataxia type 3 [SCA-3]), a progressive condition with brainstem as well as cerebellar, spinal cord, and peripheral nervous system pathology [3]. RBD is common among patients with SCA-3 [4]. In this case, episodes of prolonged nocturnal wandering that were often violent began 15 years prior to the diagnosis of SCA-3. PSG demonstrated multiple behavioral events from NREM sleep and during REM sleep together with REM sleep without atonia (RWA) [3]. (2) A 49-year-old man with a 23-year history of nightly violent sleep-related episodes was initially misdiagnosed to have pseudo-seizures and recurrent non-epileptic spells, but eventually had vPSG confirmation of POD; bedtime clonazepam therapy was immediately effective in controlling the parasomnia, as confirmed by the patient's wife and by follow-up vPSG 2 months later [5].

27.2 Update and Current Classification of POD

Since 1997 the growing literature on POD has expanded in at least three novel directions: (1) Appetitive NREM sleep parasomnias (sleep-related eating disorder [SRED] [6]; sexsomnia/sleep sex [7–9]) are now linked with RBD in POD; (2)

rhythmic movement disorder (RMD) is now linked with RBD in POD [10]; (3) additional types and CNS locations of symptomatic cases have been identified. Table 27.1 contains the current classification of POD and provides a framework for anticipating additional categories of POD, such as the following three clinical variants: (1) one patient in a series of five idiopathic POD (iPOD) patients [11] probably had a novel variant of POD involving sleep-related dissociative disorder [12–14], in addition to RBD and SW, as described below; (2) a patient with a NREM parasomnia who receives pharmacotherapy with an SSRI or venlafaxine for an anxiety or depressive disorder could then develop medication-induced RBD [15] as a secondary form of POD; and (3) a patient with RBD who is treated for insomnia with zolpidem or another hypnotic could then develop a NREM parasomnia (disorder of arousal; SRED [16]) as a secondary form of POD.

27.3 Idiopathic POD (iPOD)

A patient is given a diagnosis of iPOD when ICSD-3 diagnostic criteria for both RBD and a NREM parasomnia are satisfied [2] in the absence of an underlying neurological/psychiatric condition or a plausible inducing medication. Over the years several case series have begun to define the presentation, prevalence, and course of iPOD. Those reports will now be summarized.

Cases of presumed iPOD were reported decades ago in Japan, involving dream enactment consistent with RBD and sleep-related ambulation [17, 18]. Since walking during RBD in humans is uncommon and leaving the bedroom is very uncommon, it appears that in at least one of these cases the nocturnal walking represented SW as a NREM sleep parasomnia in a patient with POD [17], and in three other cases there was insufficient information provided to determine whether the walking was from RBD, or from SW as part of POD [18].

iPOD (RBD with SW) was diagnosed in 15 patients from a series of 91 RBD patients in which the vPSG and clinical data were compared between RBD patients diagnosed before or after age 50 years [19]. In the younger group, 65% (13/20) of patients with idiopathic RBD (iRBD) also had SW/POD, whereas in the older group, only 6% (2/33) of iRBD patients also had SW/POD. All the POD patients could be easily awakened from RBD episodes and had clear recall of the dreams they were enacting. In contrast, during their NREM sleep parasomnia episodes with SW and sleep talking, they could not be easily aroused, had no dream recall, and had poor recollection of these events. These striking, age-related POD findings raise questions about the age of onset, longitudinal course, and natural history of POD, in regard to both the RBD and NREM parasomnia components of POD. Similar developmental questions were raised in the context of RBD associated with narcolepsy that also demonstrates an earlier age of onset [20].

Five cases of iPOD were reported in a series of 11 cases of REM sleep without atonia (RWA), with both RBD behaviors and NREM parasomnia behaviors confirmed by vPSG [21]. Clonazepam at bedtime successfully controlled the POD. In a series of 93 RBD patients, POD was diagnosed in two patients and probable POD (not confirmed by vPSG) in another 8 patients (for a total of 11% [10/93])

who reported confusional arousals and SW besides typical RBD behaviors; however, the distinction between iRBD vs. symptomatic RBD/POD cases was not addressed [22].

In a retrospective study of 70 Chinese-Taiwanese RBD patients (64% male) with mean age of RBD onset of 60 years (range 20–75 years), 18 patients (26%) were reported to have nocturnal ambulation, with 11 patients wandering in the bedroom and 7 patients wandering out of the bedroom [23]. Dream enactment with the wandering was not addressed, nor was the age of onset of the nocturnal wandering reported. Also, there was no distinction reported in nocturnal wandering between the iRBD vs. symptomatic RBD groups, with the latter group comprising 66% (46/70) of the RBD series. Therefore, an indeterminate number of these RBD patients may have had POD, with SW being the likely cause of the nocturnal wandering, particularly in those patients with Parkinson's disease (PD) who have been shown to be at risk for POD (SW-RBD), to be discussed below.

A report on a case series of five iPOD patients (3/5 females, age 21–72 years) raised the question of whether POD is a distinct pathophysiological entity and not just a variant of RBD [11]. In all of five patients, RBD was less prominent than the disorder of arousal. In two patients, RBD symptoms became exacerbated after the start of antidepressant medications. In two other cases, although RBD symptoms compared to the two cases just described were more prominent (without any exacerbating factor), nevertheless their NREM parasomnias were more long-standing, frequent, and injurious. One case involving a 36-year-old woman may have represented a novel subtype of POD involving RBD/NREM parasomnia/sleep-related dissociative disorder (S-R DD). She had a history of prior repeated physical abuse inflicted by an ex-husband. She reported nocturnal wandering every night and frequently left the house. She also smoked, cleaned, and engaged in complex tasks for which she had no recollection the following morning. During vPSG, behavioral events emerging from N2 arousals supported the diagnosis of a NREM parasomnia, rather than sleep-related dissociative disorder, in which there is sustained EEG wakefulness out of N1 or N2 sleep lasting 30–60 s before the start of any behavioral activity [12]. Nevertheless, due to her compelling history consistent with having occasional events of S-R DD, she was presumed to have a combination of SW and wandering related to S-R DD. The authors proposed that given the younger age of onset of iPOD compared to RBD, the prominence of NREM parasomnia symptoms over RBD symptoms, and the lack of proven longitudinal correlation with underlying neuropathology in iPOD (compared to iRBD in which >80% of patients older than 50 years will eventually develop alpha-synucleinopathy neurodegeneration [24, 25]), then iPOD may represent a distinct diagnostic entity. They suggested that POD may represent an evolution of sleep-related motor-behavioral dyscontrol over the life cycle, with the NREM parasomnia component being more prominent earlier in life and RBD being more prominent in later life. This point was raised in a recent case report of POD involving a 53-year-old woman with onset of a NREM parasomnia at the age of 20 years, with vPSG confirmation of her NREM parasomnia 33 years later, along with confirmation of preserved REM-atonia and absence of RBD [26]. However, after 7 years she was documented by vPSG to have also

developed the dream enactment of RBD, with increased phasic EMG activity during REM sleep along with punching and prominent limb jerking. Of note, she had been treated with paroxetine for 10 years, i.e., beginning 3 years before the first vPSG study that ruled out RWA/RBD, and so it appeared unlikely that chronic paroxetine therapy played a role in the future emergence of RBD. On examination she did not demonstrate abnormalities consistent with a neurodegenerative disorder.

Finally, an extraordinary case of POD was recently reported in a 63-year-old Chinese man with POD onset at age 11 years, manifesting as aggressive dream-enacting behaviors and SW [27]. The POD intensified over time with increased frequency of the RBD behaviors (1–2 nights/week) and with eventual waning of SW by around age 40 years. Aggressive behaviors included severe repeated biting, shouting, throwing punches, kicking, and leaping from bed. An example was given of sleep biting with dream enactment: "One night, he dreamed that he was eating an apple, but instead, he was biting his wife's ear. After that night, during similar dreams, he would bite her ears, and her nose and face, which resulted in the end of their marriage after four years (age 28)." He was married a total of 4 times (for 1.5, 2.5, 4, and 10 years) and was divorced all 4 times because of these aggressive sleep and dream behaviors, including severe injurious biting. An additional three relationships also ended for the same reason. RBD was vPSG confirmed. Neurologic exam was unremarkable. MMSE score was 27, and ESS score was 7. There were no psychiatric or drug abuse history and no prior exposure to psychotropic medication.

27.4 Symptomatic POD

The most common disorders associated with POD are disorders of alpha-synuclein neurodegeneration. Other cases are typically either medication induced or related to brainstem pathology. Case reports and case series of symptomatic POD are summarized below.

Additional symptomatic cases of POD since 1997 have included several categories of neurologic disorders, including PD and related disorders. In the first of three studies of PD by the Bassetti group, six patients had developed adult-onset SW either after the onset of PD ($n = 4$) or with the onset of PD ($n = 2$); four of these patients also had RBD and therefore had POD [28]. In this retrospective study, *de novo* SW was detected in 3.6% (6/165) of consecutive patients with PD. The second study was a prospective questionnaire-based survey of SW in PD, which found that 9% (36/417) of PD patients reported SW—including 5% (22/417) with adult-onset SW [29]. Of these 36 PD-SW patients, 26 (72%) also had presumed RBD/POD. The third study [30] involved vPSG studies performed in 30 PD patients from the previous questionnaire study [29]: $n = 10$ PD-SW, $n = 10$ PD-presumed RBD; $n = 10$ PD-no parasomnia history. vPSG studies documented RBD/POD in 80% (8/10) of the PD-SW patients.

POD emerging with acute rhombencephalitis was reported in a 40-year-old woman with a right pontine tegmentum/medulla lesion being sufficient to cause bilateral RBD dream-enacting behaviors, along with ataxia, eye movement

abnormalities, and multiple cranial nerve abnormalities [31]. vPSG revealed sudden arousals from N3 sleep as well as increased tonic and phasic chin muscle tone during REM sleep with dream enactment behaviors, diagnostic of both a NREM parasomnia and RBD. The findings were correlated with a unilateral lesion near the subcoeruleus nucleus, a region whose disturbance can induce RBD.

A possible case of POD has been reported in an 88-year-old man with Alzheimer's disease and rivastigmine-induced RBD and walking/wandering behavior that may have been SW as a comorbid secondary NREM sleep parasomnia [32].

In a series of 19 consecutive cases of subclinical RBD (excessive tonic and/or phasic EMG activity in REM sleep without clinical RBD behaviors), 9 had a POD variant, viz., subclinical RBD-NREM sleep parasomnia [33]. All 19 cases of subclinical RBD occurred with conditions involving motor dyscontrol across sleep and wakefulness: NREM parasomnias (SW, sleep terrors); narcolepsy; periodic movements of sleep; olivopontocerebellar atrophy (OPCA); obstructive sleep apnea (OSA) with agitated arousals; and fluoxetine therapy of major depression (inducing NREM sleep oculomotor dyscontrol with prominent eye movements [34]). Excessive phasic electromyographic (EMG) twitching in REM sleep was found in 16/19 patients, and excessive tonic submental EMG activity was found in 10/19 patients (4/9 with NREM parasomnias; 4/6 with narcolepsy; 1/1 with OPCA; 1/1 with fluoxetine therapy). Subclinical RBD-POD was also reported in a group of 33 patients with NREM parasomnias and excessive tonic and phasic EMG activity during REM sleep, but without release of RBD behaviors [35]. A recent study has extended the findings on REM sleep motor dyscontrol in NREM parasomnia patients [36]. This study by the Arnulf group in Paris had 251 subjects: RBD, $n = 64$ [29, iRBD; 35, RBD-PD]; NREM parasomnia (SW, ST), $n = 62$; older healthy controls, $n = 66$; and young healthy controls, $n = 59$. NREM parasomnia patients scored positive for RBD in a screening test, thereby diminishing the specificity of the RBD screening test. These NREM parasomnia patients also had increased phasic EMG activity in REM sleep compared to controls, but without any increased tonic EMG activity in REM sleep.

Three cases of POD associated with PD have recently been reported in two men and a woman, 55–75 years old [37]. They underwent bilateral subthalamic deep brain stimulation (DBS). The first two cases had opposite results from DBS on their POD, with the first case obtaining substantial benefit and the second case deteriorating. The POD also deteriorated after DBS in the third patient. Worsening outcome of POD after DBS was speculated to be due to either the DBS (and its exact location), role of medication, or disease progression. The authors called for "more detailed and broad-spectrum assessments regarding parasomnia in PD patients that undergo DBS."

A variant form of autoimmune POD with RBD, abnormal behaviors emerging with greatly disturbed NREM sleep, and sleep-related breathing dysfunction (OSA, stridor) was recently reported in a carefully documented case series of eight patients, including postmortem analyses, that was associated with antibodies to IgLON5 [38].

Numerous additional cases have been published on what is now referred to as anti-IgLON5 syndrome. Neuropathology detected a tauopathy, with neuronal loss and extensive deposits of hyperphosphorylated tau primarily involving the tegmentum of the brainstem and hypothalamus in the two patients studied. This major discovery, along with the additional published cases, will be discussed in detail by Iranzo in Chap. 8 (RBD Associated with Paraneoplastic Syndromes and Autoimmune Disorders). POD was also reported in two cases of Harlequin syndrome (asymmetric sweating and flushing of the face and upper chest) affecting two women, aged 52 and 66 years [39]. Of note was that their POD was found to be an evolving status dissociatus (discussed in Chap. 28).

27.5 POD with Appetitive Parasomnias: Sleep-Related Eating Disorder-RBD and Sexsomnia-RBD

SRED is considered to be an appetitive behavior on the basis of the individual seeking out food to eat, primarily taking the form of leaving the bed while asleep and going to the kitchen to find and consume food, with diminished or absent consciousness and subsequent recall. SRED is classified as a NREM sleep parasomnia in the ICSD-3 [2]. A case of SRED combined with RBD was reported in a 37-year-old man with early-onset (age 32 years) PD [6]. SRED emerged 4 years after PD onset. RBD manifesting with violent dream enactment began 15 years previously, i.e., 10 years before PD onset. This man also had a childhood history of SW and sleep terrors. Four cases of sexsomnia/sleep sex associated with RBD (including one case with probable RBD) have also been reported: a 60-year-old woman (who also had SRED) and 27-, 41-, and 42-year-old men [7–9]. Three of these patients each suffered from five distinct parasomnias [8, 9], including RBD, SW, sleep terrors, SRED, sleep sex, and sleep talking, and one patient had three parasomnias, including presumed RBD (with violent dream enactment), SW, and sleep sex [7]. In one case, obstructive sleep apnea was triggering the SW and SRED, as nasal CPAP therapy resolved these two NREM parasomnias, and bedtime clonazepam therapy substantially reduced the frequency of sexsomnia [9]. These four cases illustrate how sleep sex usually emerges in the context of a long-standing, complex parasomnia history, or else with more recent-onset OSA that presumably triggers sexual behaviors during apnea-induced partial arousals. Sexsomnia is a recognized subtype of confusional arousals and sleepwalking, i.e., disorders of arousal from NREM sleep, in the ICSD-3 [2], and its designation is “sleep-related abnormal sexual behaviors.” Reported cases have been male-predominant, and the problematic behaviors include prolonged or violent masturbation, sexual molestation and assaults (of bed partners/minors), initiation of sexual intercourse, kinky/peculiar sex, and loud/offensive sexual vocalizations during sleep, followed by morning amnesia [40].

Table 27.2 Familial parasomnia overlap disorder (spectrum of motor-behavioral dyscontrol across REM sleep, NREM sleep, and wakefulness in three first-degree family relations)[a]

Categories	Son	Uncle/brother	Father
Age, years	22	46	49
Age, onset of sleep motor dyscontrol, years	5	36	31
Restless legs syndrome (legs, arms, whole body)	–	+	+
Periodic limb movements of NREM sleep[b]	+	–	+
Aperiodic limb movements, NREM sleep	–	+	–
Sleepwalking/sleep terrors (NREM sleep parasomnias)	+	+	–
RBD (REM sleep behavior disorder)	–	–	+
Sleep paralysis (with narcolepsy)	+	–	–

Adapted from [42] (Table 2)

[a]They each underwent two consecutive overnight video-polysomnographic (vPSG) studies and a daytime multiple sleep latency test, while receiving no medications for ≥1 month

[b]Periodic limb movements of NREM sleep hourly index (usually with arousals), during the first and second vPSG studies: Son, 26/h ($n = 195$) and 14/h ($n = 44$); father, 42/h ($n = 383$) and 33/h ($n = 184$)

27.6 POD: Rhythmic Movement Disorder (RMD)-RBD

POD manifesting as RBD with RMD [2] was described in two male patients, 55 and 56 years old, with 2–9-year histories of typical RBD dream-enacting behaviors [10]. vPSG detected the EMG and behavioral findings of RBD. Each patient also demonstrated recurrent, short-lasting episodes of rhythmic head movements. One patient had two episodes of head rolling lasting 3 and 8 s, at a frequency of 2.5 Hz, which emerged during RBD episodes. The other patient had one episode of head rolling lasting 10 s, at a frequency of 1.5 Hz, which emerged during a RBD episode with prominent twitching of the lower limbs. The authors commented on how with RBD there is dysfunction of neuronal circuits subserving REM-atonia and phasic motor-behavioral control during REM sleep, which may involve the central pattern generator neuronal networks [41] leading to the activation of rhythmic movements (head rolling) during RBD episodes.

Table 27.2 provides a striking example of familial overlapping parasomnias [42]. Members of this family displayed a wide spectrum of state boundary and motor-behavioral dyscontrol across six clinical categories. Each of the three first-degree relations had sleep-related motor-behavioral dyscontrol in three of the six categories. Parasomnia behaviors were controlled with bedtime benzodiazepine therapy.

27.7 Therapy of POD

Management of POD should first focus on resolving comorbid conditions that fragment sleep, such as sleep-disordered breathing, and discontinuation of any suspected precipitating or aggravating medication. Clonazepam taken at bedtime (0.5–1.0 mg) is usually effective in controlling RBD and a NREM parasomnia (SW, sleep terrors, sexsomnia), with SRED requiring separate therapy, such as with topiramate [43]. For

medication-resistant patients, a customized bed alarm may help prevent sleep-related injury in RBD [44]. A second case of hypnosis has been reported to be effective in a case of POD involving a 16-year-old male patient with SW, sleep talking, and RBD dream enactment [45]. Three sessions of hypnosis treatment with teaching of self-hypnosis resulted in sustained benefit for 5 years, at the latest follow-up. Finally, as stated above, DBS therapy of PD in three patients with comorbid POD had very different POD outcomes among the three patients [37].

Conclusion

More than 150 cases of POD/probable POD have been published to date, with more than half being iPOD cases and the rest being symptomatic POD across a spectrum of clinical disorders. The current updated POD classification, listed in Table 27.1 and described in the text, further supports the hypothesis that POD is not simply a subtype of RBD but a distinct pathophysiological entity [11]. Furthermore, some subtypes of POD appear to occur more frequently in early-onset RBD than others. Further study is needed to determine whether age and gender affect the variants of POD. A search for familial POD is also warranted. Possible underlying mechanisms of POD have been discussed [1], which need further elaboration to include appetitive parasomnias, RMD, and the symptomatic causes described in this chapter. Since to date there are no data indicating an increased risk for phenoconversion from POD to neurodegeneration, as is found in RBD in middle-aged and older patients [24, 25], patients diagnosed with POD should be reassured, albeit with caution, and their physicians advised to perform periodic neurological examinations. Moreover, the literature reviewed herein encourages a careful search for RWA and mild RBD (i.e., POD) in patients with NREM parasomnias. Finally, the most extreme form of POD with abnormal behavioral release that emerges with complete sleep-wake state boundary dyscontrol is status dissociatus [42, 46], which is the topic of Chap. 28.

Note Added in Proof: An additional novel case of POD has been published, involving Creutzfeldt-Jakob disease [47].

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Status Dissociatus and Its Relation to RBD

28

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Abbreviations

ADCA-DN	Dominant cerebellar ataxia, deafness, and narcolepsy
caspr2	Contactin-associated protein 2
CSF	Cerebrospinal fluid
EEG	Electroencephalography
EMG	Electromyography
GBS	Guillain-Barré syndrome
Hcrt	Hypocretin
Lgi1	Leucine-rich glioma-inactivated 1
MSA	Multiple system atrophy
NT1	Type 1 narcolepsy
NMDA	Anti-*N*-methyl-D-aspartate
PD	Parkinson's disease
PLMs	Periodic leg movements
PSG	Polysomnography
RBD	REM sleep behavior disorder
REM	Rapid eyes movement
RSWA	REM sleep without atonia
SD	Status dissociatus
SOREMP	REM sleep onset periods
VGKC-Ab	Voltage-gated potassium channel complex antibodies
W	Wake

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28.1 Introduction

Status dissociatus is an umbrella term aimed to label different disorders that share as a main feature the vulnerability of "state boundaries." Each state of being is conventionally defined as a recognizable cluster of behavioral, neurophysiological, and autonomic descriptors, occurring over a designated period. Indeed, it is the combination of different parameters, both behavioral and neurophysiological (i.e., EEG, EOG, EMG, ECG, etc.), which empirically identifies clusters defining the different states of being, i.e., wakefulness, rapid eye movement (REM) sleep, and NREM sleep. Each descriptor taken by itself is deceptive in defining a state, as, for example, changes in EEG do not always reflect changes in state (e.g., as seen with the fast rhythms in benzodiazepine-induced sleep or the postictal slow rhythms), and the same applies for the behavioral counterpart (e.g., as seen with enacted dreams).

Status dissociatus represents the result of the breakdown within the association of the different descriptors defining each cluster, resulting in the asynchronous occurrence of the various components of the different states of being, and therefore preventing the recognition of conventionally defined states of being over an established time span.

The term "status dissociatus" was first coined by Raynal [1] to indicate a polysomnographic trait in tricyclic-medicated narcoleptic patients. However, the concept of status dissociatus emerged and was more extensively elaborated with the first case series reported in 1991 by Mahowald and Schenck [2]. At that time, the authors described six patients affected with a severe state dissociation, i.e., quoting the authors, "ambiguous, multiple or rapid oscillation of state-determining variables with simultaneous appearance of elements of all three states, and with the only full-declared state being wakefulness," due to different underlying conditions [2].

28.2 Dissociation of States and Status Dissociatus

The chapter encompasses both "dissociation of states" and "status dissociatus—SD."

With the term "dissociation of states," we refer to paraphysiological or pathological conditions, characterized by the occurrence of episodes due to the transient and usually brief intrusion of features of a state into an ongoing main state. The term "status dissociatus" will instead be used for pathological conditions where recognizable cluster descriptors are lost or with subcontinuous state transitions.

For the first category, we will adopt the original classification proposed by Mahowald and Schenck [2]. Indeed, in their original description and seminal introduction to this novel concept, the authors (1991) classified three types of dissociation of states based on the parent (or main) state: i.e., dissociation from prevailing wakefulness, dissociation from NREM sleep, and dissociation from REM sleep. For SD, we will refer to the classification recently proposed [3], distinguishing two main subtypes of SD, i.e., the classically defined-severe SD and the

intermittent-intermediate one. Of course, both classifications carry the birthmark of all the classifications trying to fit the complexity of human physiological and pathological conditions in conventional boxes.

28.2.1 Dissociation from Wakefulness

These conditions are the result of the intrusion of other states of being into wakefulness.

They include conditions characterized by admixture of mentation of wake and sleep, like hypnagogic or hypnopompic hallucinations, nocturnal hallucinations, and automatic behaviors.

Hallucinations at the wake-sleep transition are typically seen in narcolepsy (ICSD, 3 ed.; [4]) but can occur also as the consequence of alcohol/drug intoxication or withdrawal, brainstem or thalamic lesions, severe visual loss (Charles Bonnet syndrome), and of other neurological conditions, such as neurodegenerative conditions [5] or autoimmune encephalitis [4].

Transient admixtures of states of being might occur also in the normal population at wake-sleep transitions, especially during childhood or in the setting of sleep deprivation or stressful events, resulting in somatosensory illusions or hallucinations [6].

Automatic behaviors are another example of such dissociation, characterized by the occurrence of inappropriate action or pronunciation of "out-of-context" sentences while awake and reputedly related to a brief dream mentation. They are mainly observed in the context of pathological conditions, such as idiopathic hypersomnia and narcolepsy, but rarely they may be experienced also by healthy individuals [4] and mainly in subjects who are severely sleep deprived.

It may also happen that the body is "asleep" (paralyzed) while the mind is awake, as in cataplexy and sleep paralysis. Cataplexy is the typical motor feature of type 1 narcolepsy (ICSD, 3rd ed.). Sleep paralysis is instead a conscious state of involuntary immobility typically arising on awakening from REM sleep or at the beginning of a REM sleep onset period and due to persistence/anticipation of REM sleep atonia (ICSD, 3rd ed.). It can occur rarely in healthy subjects, but it is more frequent in conditions of central hypersomnia (e.g., type 1 narcolepsy—NT1).

28.2.2 Dissociation from NREM Sleep

Admixture of wakefulness and NREM sleep results in a NREM parasomnia, which may present with different degrees of behavioral and autonomic features and include a spectrum of overlapping conditions, such as confusional arousals, somnambulism and sleep terrors, or the peculiar behaviors described in "sleep-related eating disorder" and "sleep-related sexual activity" ([7]; ICSD, 3rd ed.).

NREM parasomnias are generally more frequent during childhood but may persist or even arise during adulthood [8]. Hereditary factors have been strongly implicated in sleepwalking and sleep terrors, and specific DQB1 genes were implicated

in a study of 60 Caucasian subjects with different types of NREM parasomnia and their families [9], as well as the first genetic locus for sleepwalking being found at chromosome 20q12-q13.12 in an extended family pedigree with sleepwalking. Episodes may be precipitated by external triggers (sleep deprivation, sleeping in novel or other particular settings, noise, etc.) or by internal triggers (anxiety, stress, fever).

Subjects typically present with eyes open and preserved ability to move or (limited) to interact with the environment while performing inappropriate behaviors. Scalp EEG shows admixed features of NREM sleep. The intracerebral EEG recording capturing an episode of confusional arousal in an epileptic patient showed EEG features of W over the motor and cingulate cortices, concurrent with delta activity over the frontoparietal associative cortices [10], while a study with single-photon emission computed tomography during an episode of sleepwalking showed activation of thalamo-cingulate pathways and persistent deactivation of other thalamocortical arousal systems [11]. Recently, a gray matter volume decline in the dorsal posterior and posterior midcingulate cortex at the brain MRI has been found while comparing 14 patients with NREM parasomnia versus healthy controls [12], as a possible anatomical substrate explaining simultaneous coexistence of different states of being, i.e., wakefulness originating from the motor and cingulate cortices and sleep in associative cortical regions.

28.2.3 Dissociation from REM Sleep

RBD, due to incomplete declaration of REM sleep because of the intermittent lack of REM sleep muscle atonia (RSWA), is the most well-known example of this subtype of dissociation of states. Put into simple words to explain the concept, in RBD, the mind is asleep (REM dream mentation) while the body is awake (spinal motor neurons are still excitable).

RBD may present as an acute phenomenon or as a chronic disorder. We will not report on RBD here, but we want just to remark that similarly to status dissociatus, transient RBD has been described in the context of autoimmune diseases ([13–18]; see also Chap. 8 of the current textbook).

A further condition fitting in this box is lucid dreaming, which consists of the experience of being aware of dreaming (and often directing the dream) while being asleep (REM sleep) [19, 20].

The experience of lucid dreaming is quite frequent in the younger population, as pioneering studied by La Berge in the early 1980s [20], and it has been reported to be even more frequent in narcoleptic patients [19].

28.3 Status Dissociatus

SD labels the extreme degree of severity of dissociation states, which can be either continuous with the complete breakdown of state-determining boundaries and aberration of state descriptors or may occur intermittently and still preserve recognizable, although at times ambiguous, state descriptors.

In 1991, thanks to Mahowald and Schenck, status dissociatus was theorized as a condition characterized by ambiguous oscillations of state-determining variables with the simultaneous appearance of elements of all three states of beings. In their original report, the authors reported this status to occur in six patients affected with different underlying neurological conditions (i.e., chronic alcohol abuse and acute withdrawal, olivopontocerebellar atrophy, cardiac surgery-related central nervous system anoxic injury, OSA/narcolepsy-cataplexy with methylphenidate/imipramine therapy, and narcolepsy-cataplexy with methylphenidate/imipramine therapy).

A breakthrough on this matter was made by Elio Lugaresi in 1986 with the description of fatal familial insomnia and, years later [21–23], by coining the term "agrypnia excitata," to describe the extreme dissociation state that they observed in fatal familial insomnia and to some extent also in alcohol withdrawal syndrome and Morvan's syndrome. All these three different conditions indeed are examples of an extremely severe dissociation, sharing the presence of the inability to generate and sustain sleep, accompanied by severe mental confusion and motor and autonomic hyperactivity [23].

Nowadays, we might say that while Mahowald and Schenck [2, 24] described conditions mainly ascribed to the intermittent/intermediate form of SD, Lugaresi et al. [25] reported the first case of a severe and continuous SD.

In the current ICSD3, SD is classified among the subtypes of RBD (ICSD, 3rd ed.).

According to a recently proposed classification [3], it is possible to recognize two main subtypes of SD, i.e., the classically defined-severe subtype and the intermediate-intermittent subtype.

28.3.1 Classically Defined/Severe Status Dissociatus

This subtype of SD was firstly spotted by the Bologna Group [21–23] under the name of "agrypnia excitata," from ancient Greek (*agreo*, to chase, and *hypnos*, sleep), which meant to indicate loss of sleep [26].

The term aimed at synthesizing the common discrete features of three different conditions, i.e., fatal familial insomnia, alcohol withdrawal syndrome, and Morvan's syndrome. All these conditions shared a similar phenotypic features and clinical markers, even if the etiologies and the neurophysiological backgrounds may be different among each other (see later).

Fatal familial insomnia is an autosomal dominant prion disease with selective thalamic and inferior olivary degeneration [25], due to a missense mutation at codon 178 of the prion protein gene co-segregating with methionine (met) at methionine-valine (Val) polymorphic codon 129 in the mutated allele [27]. Patients may have a short (from 8 months) or a prolonged (up to 72 months) clinical course according to whether they are homozygote met/met or heterozygote met/val at codon 129.

Morvan's syndrome is a rare autoimmune disease, due to contactin-associated protein-like 2 (caspr2) antibodies subtypes of antibodies to the VGKC. The main clinical features are acute or subacute onset of insomnia, nearly continuous muscle activities (myokimias and cramps), autonomic imbalance, and pain in the

extremities [21, 28, 29]. Plasma exchange or intravenous immunoglobulins are usually efficacious within a few months, except for few non-responder cases, where a progressive worsening until death has been reported [21, 29].

Finally, alcohol withdrawal syndrome (delirium tremens) brought about by sudden alcohol withdrawal in alcohol abusers [2, 30] is characterized by the acute-subacute onset of a nearly continuous status during which the patients present with tremors, nausea, anxiety, insomnia, motor, and autonomic activation with agitation and hallucinations. In this condition, the dream enactment is mainly violent, but an eventual pattern with calmer gestures has been reported [30]. A similar condition may occur after withdrawal from meprobamate, barbiturates, and benzodiazepines (ICSD, 3rd ed.).

All these three conditions combine organic insomnia (i.e., the inability to initiate and sustain sleep) with a confusional-oneiric state, together with motor hyperactivity, autonomic hyperactivity (with tachycardia, tachypnea, hypertension, fever, hyperhidrosis, etc.), and persistently (through the 24-h) increased blood cortisol and plasma catecholamine when compared to normative values [23, 31]. Both the cyclic structure of sleep and the circadian rhythmicity are lost [31]. The disease usually starts with reduced sleep time, hypnagogic hallucinations, and RBD, until reaching the full-blown state during which patients spend most of the time in a state of sub-wakefulness with the EEG showing features of stage 1 of NREM sleep, while spindles and delta activity were lost. Neurophysiological features of REM sleep persist but occur mainly in the form of "covert" EEG REM sleep or REM sleep without atonia and in short recurrent episodes, isolated, or mixed with stage 1 NREM potentials (Fig. 28.1). Clustered REM sleep episodes frequently coincide with gestures mimicking task-oriented daily life activities, such as dressing, combing the hair, washing, or manipulating an imaginary object. These episodes may also occur with open eyes. If questioned at the end of these behaviors, patients often do not admit that they were asleep, although they link these gestures to an oneiric/hallucinatory scene, and the motor activity appears to be clearly related to the oneiric/hallucinatory content. This peculiar behavior, named "oneiric stupor," represents in fact the motor and behavioral marker of *agrypnia excitata* [23] (Fig. 28.2).

*"*Oneiric stupor*"* with the subcontinuous gesturing that mimics almost purposeful behavior of daily life is different from the typical energetic and vivid quality of RBD episodes. This is mirrored by the different mentation reported in these conditions, i.e., patients usually describe an ordinary scene of daily life in *agrypnia excitata*, in contrast to a bizarre, complex, and vivid scene in RBD.

Agrypnia excitata has also been reported in two unrelated cases affected by Mulvihill-Smith syndrome, which is a rare and complex congenital neurodegenerative disease, characterized by a progeria-like aspect, peculiar multiple pigmented nevi, low stature, and cognitive impairment leading to premature death [32, 33].

Features of *agrypnia excitata* have been observed also in the sporadic and in the variant forms of Creutzfeldt-Jakob disease and as a consequence of CNS lesions, but apart from the cases where a clear and prominent thalamic involvement was reported, they did not reach the full-blown clinical picture.

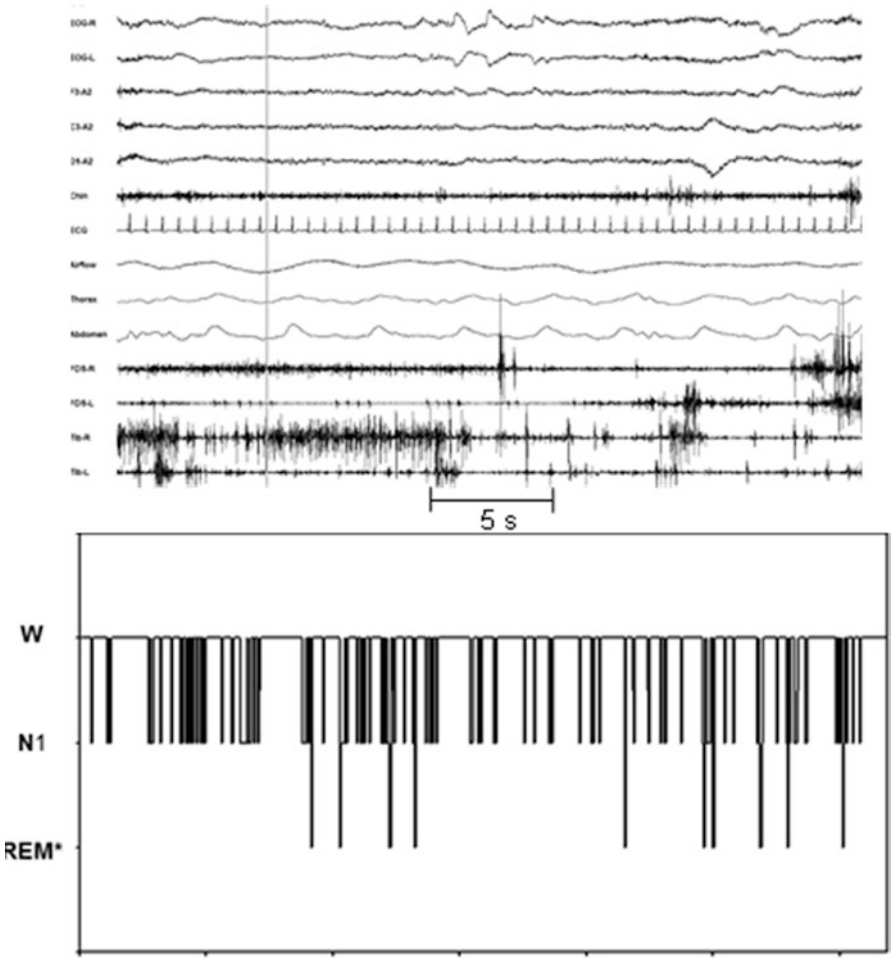

Fig. 28.1 Hypnogram of 24-h duration, in a patient affected with autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) due to DNMT1 gene mutation. Ordinate (y) reports the time of the day. *W* wakefulness, *R* REM sleep, *1* stage 1 of NREM sleep, *2* stage 2 of NREM sleep, *3* stage 3 of NREM sleep

Recently, a case of SD with cortico-basal degeneration, and with neuroimaging and anatomopathological documentation showing neurodegeneration with neuronal and glial tau deposition within the thalamus, has been described [34]. It has been suggested that neurodegenerative conditions may at time evolve into a condition of severe SD [34, 35]. Indeed, the severe metabolic and structural damage involving the CNS system may progressively render the network orchestrating the states of being powerless. In this regard, we have recently observed a patient affected with dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) due to DNMT1 mutation, who at the very end stage of the disease prior to passing away had

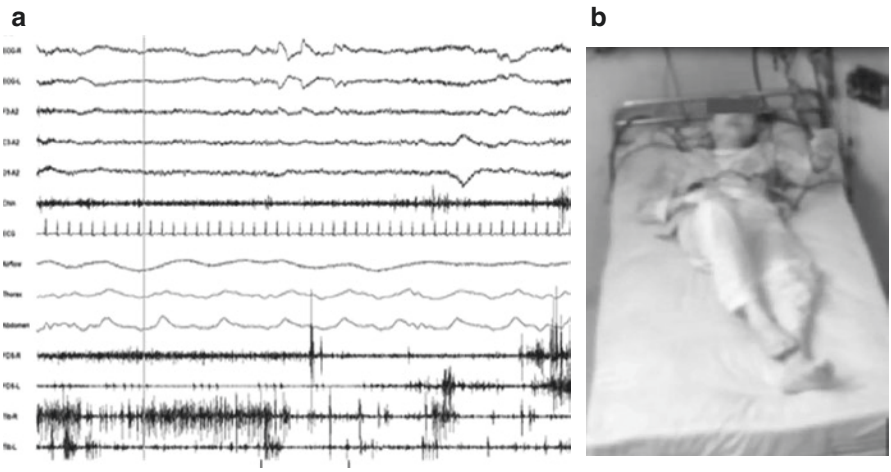

Fig. 28.2 Polygraphic features of status dissociatus in a patient affected with Morvan's syndrome. (**a**) A 30-second epoch showing admixtures of stage 1-REM sleep in the EEG tracing. (**b**) Hypnogram of the same patient

continuous state transitions with poorly recognizable state descriptors (Fig. 28.3), and he was in a nearly continuous hallucinatory state accompanied by subcontinuous gesturing [unpublished findings].

28.3.2 The Intermittent/Intermediate Status Dissociatus

In this subtype, state descriptors and proper states of being are still recognizable, but subcontinuous paroxysmal shifts versus ambiguous states of being occur, with consequent extremely fragmented and abnormal W, NREM, and REM sleep architecture. The circadian pattern might be impaired but never reaching the degree of severity seen in "agrypnia excitata."

The typical example of this subtype is found in NT1 or in conditions described in the context of autoimmune encephalitis.

NT1 is a central hypersomnia due to a deficiency of hypothalamic hypocretin 1 (orexin) signaling, of a likely autoimmune etiology (ICSD, 3rd ed.). Loss of boundaries between sleep and wake, with frequent state transitions and intrusions of REM sleep into the other ongoing states of being [36], is the neurophysiological hallmark of NT1, resulting in a pentad of symptoms, including cataplexy, excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep (ICSD, 3 ed.).

Cataplexy, sleep paralysis, hallucinations, and automatic behaviors are examples of wakefulness dissociation, while lucid dreaming and RBD are examples of REM dissociation.

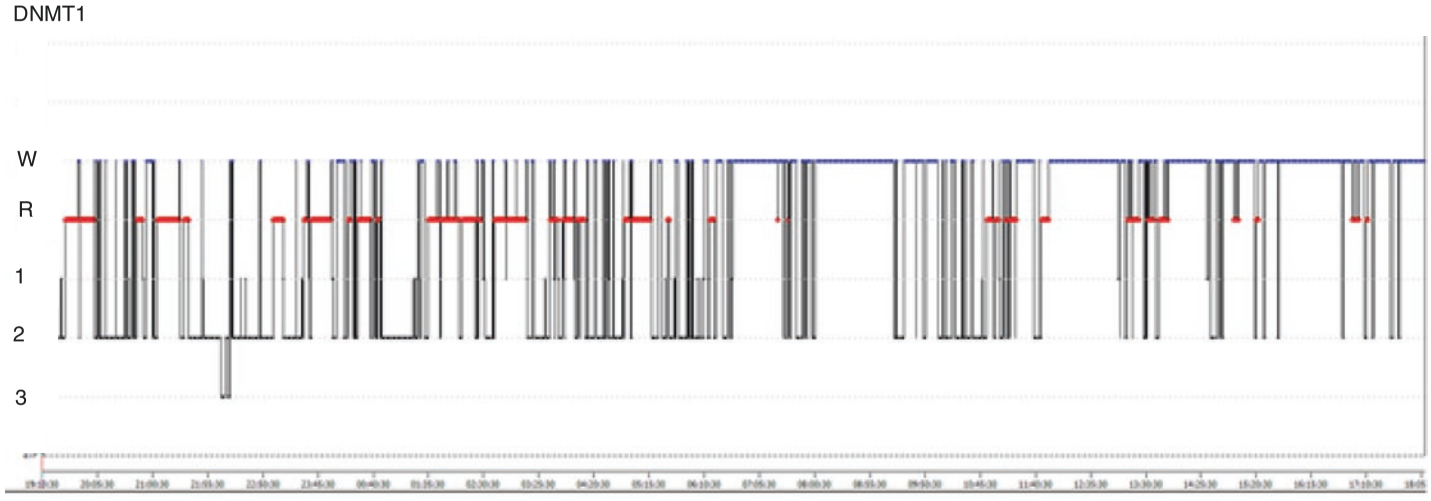

Fig. 28.3 Polygraphic and behavioral features of status dissociatus in a patient affected with Morvan's syndrome. EEG channels (Fp2-F4; F4-C4; C4-P4; P4-O2; Fp2-F8; F8-T4; T4-T6; Fz-Cz; Fp1-F3; F3-C3; C3-P3; P3-O1; Fp1-F7; F7-T3; T3-T5); *R. EOG-A2* right electrooculogram, *L. EOG-A2* left electrooculogram, *mylo* mylohyoid muscle EMG, *R. Tib* right tibialis EMG channel, *L. Tib* left tibialis muscle EMG channel

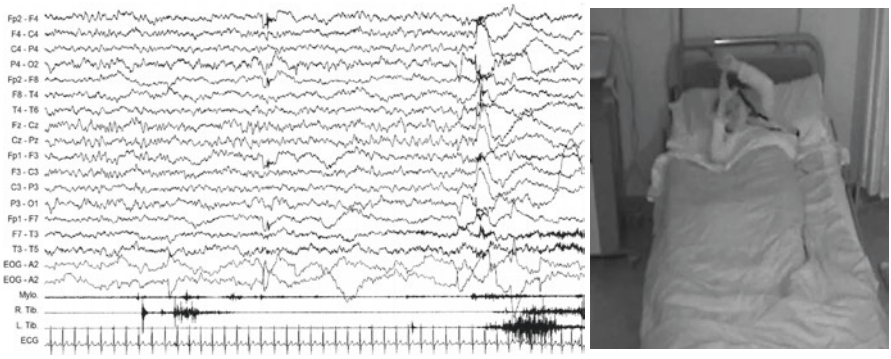

Fig. 28.4 Polygraphic and behavioral features of status dissociatus in a child affected with NT1. EEG channels (Fp2-F4; F4-C4; C4-P4; P4-O2; Fp2-F8; F8-T4; T4-T6; Fz-Cz; Fp1-F3; F3-C3; C3-P3; P3-O1; Fp1-F7; F7-T3; T3-T5). *R. EOG-A2* right electrooculogram, *L. EOG-A2* left electrooculogram, *mylo* mylohyoid muscle EMG, *R. Tib* right tibialis EMG channel, *L. Tib* left tibialis muscle EMG channel

State boundary instability in NT1 has been reported to be even more severe in children, culminating in a nearly subcontinuous state in about 30% of them. This subcontinuous state shift may emerge both from wakefulness, with what has been reported as a "cataplectic face" [37], and also from sleep with subcontinuous complex behaviors emerging from a dissociated REM sleep [38] (Fig. 28.4).

In regard to autoimmune encephalitis, sleep abnormalities have been long recognized in the context of Morvan's syndrome [21, 28, 29] and thought to be discrete of caspr2 antibody-associated encephalitis. However, recently state boundary instability and sleep disorders have also been reported in other types of autoimmune encephalitis.

Anti-leucine-rich glioma-inactivated 1 (LgI1) antibody subtypes of VGCK encephalitis are typically characterized by pathognomonic early faciobrachial dystonic seizures and other focal seizures, followed by memory disturbances [39]. In addition, insomnia along with RBD and partial loss of recognizable sleep and enacted dreams have been reported in this context [40, 41].

Anti-Ma1 and anti-Ma2 antibody-positive encephalitis are instead characterized by memory deficits, vertical supranuclear gaze palsy, excessive daytime sleepiness, diplopia, dysarthria, ataxia, parkinsonism, or hypokinesia. In a small percentage (13%) of cases, patients may have also narcolepsy with cataplexy with low cerebrospinal fluid hypocretin-1 levels (13%) [42], along with the occurrence of enacted dreams [14, 16, 43]. In such cases, PSG demonstrated severe sleep disruption, absent slow wave sleep, and sleep spindles, with subcontinuous intrusion of REM sleep into NREM sleep and complete loss of REM sleep atonia [14, 43].

Features suggestive of dissociation of states have also been reported in up to 20% of patients over a cohort of 139 patients affected with Guillain-Barré syndrome (GBS). Clinical features included hallucinations, mainly hypnagogic, and enacted dreams, while neurophysiological features consisted in fragmented sleep with

frequent state transitions and presence of RSWA [13]. Compared to patients without sleep abnormalities, CSF Hcrt A levels were reported to be reduced. Both clinical features and CSF Hcrt A levels normalize afar treatment, suggesting that GBS autoantibodies may also be causally targeting structures of the CNS [13].

Encephalopathy associated with autoantibodies to IgLON5 is a recently described syndrome characterized by a unique sleep disorder presenting with both NREM and REM parasomnias and sleep breathing dysfunction, brainstem involvement (dysphagia, dysarthria), and different combinations of movement disorders (gait problems, chorea) [44–47]. Patients usually presented with an acute or subacute onset of insomnia sleepiness and abnormal sleep-related behaviors, which can be undifferentiated NREM movements and brief and myoclonic-like RBD events or even behaviors, which share phenomenological similarities with those reported as oneiric stupor. From a neurophysiological point of view, even if NREM sleep stages 2 and 3 may be at times recognizable (though usually very disturbed), sleep architecture is unstable with frequent stage transitions and with features of different states that at times merge. Autoantibodies against IgLON5, a neuronal cell adhesion protein, and positivity to haplotypes DQB1*0501 and DRB1*1001 were detected in most of them. Their pathogenicity however is still questionable, and the disorder does not respond to immunotherapy, apart from exceptional cases [44]. Neuropathology shows a peculiar tauopathy, mainly involving the tegmentum of the brainstem and the hypothalamus [46, 48]. The association with a rare HLA subtype and the presence of specific antibodies suggest an autoimmune cause or trigger, while the chronic clinical course, poor response to immunotherapy, and pathological findings suggested a neurodegenerative process.

Clinical experience and sporadic reports suggest that an admixture of states of being may eventually occur also in critical illness due to infectious or metabolic conditions, but instrumental examinations (including video-PSG recordings) in these conditions are lacking, and this hampers any conclusion.

28.4 Pathophysiology

In this chapter, we have reported conditions characterized by dissociation of states and SD occurring in a wide spectrum of clinical conditions and therefore linked to different underlying causes. Overall, both structural and functional abnormalities involving thalamo-limbic and the brainstem structures may result in conditions characterized by state of boundary instability.

Sleep and wake states indeed are the result of the dynamic interactions within the sleep/wake circuitry [49], with the brainstem, the hypothalamus, and the basal forebrain involved in the promotion of the waking state, while structures of the preoptic area and of the contiguous basal forebrain promoting sleep. However, the ultimate mechanisms of such orchestration are still puzzling.

A great body of evidence recognizes the thalamus as the hallmark anatomical location of *agrypnia excitata*, linked therefore to the thalamo-limbic GABAergic dysfunction and to the consequent release of the hypothalamus and of the brainstem

from cortico-limbic control [23]. GABAergic impairment might be linked to different causes, such as the direct degeneration of the thalamus in FFI, autoantibodies targeting the thalamo-limbic structures in Morvan's syndrome, or acute imbalance of the GABAergic synapses in the limbic system due to a downregulation induced by alcohol or drugs.

Along with the thalamus, impairment of the network orchestrating the states of being may occur at different levels, and abnormalities within the structures that interact with the thalamus (mainly frontal and cingulate cortices) may account for SD in the different spectrum of diseases.

Neuropathological abnormalities have been reported at the level of the dorsolateral midbrain, the amygdala, the hypothalamus, and the mammillary bodies in anti-Ma encephalitis [14, 16], the neocortex, and the limbic area in anti-Lgi1 antibodies encephalitis [39] and the hypothalamus and the limbic area in GBS [13] and in NT1.

In anti-VGKC encephalitis, a direct role of potassium channels has been suggested, given the reported role of those subfamilies of VGKCs in regulating the wake-sleep cycle [41].

In NT1, a great body of literature supports the lack of Hcrt-producing cells, resulting in undetectable Hcrt-1 levels in the CSF in promoting SD.

Indeed, Hcrt-1 has a pivotal role in controlling sleep-wake transitions and REM sleep [50] and in orchestrating motor control during wakefulness and sleep [51]. Similarly, low levels of hypocretin have been also reported in patients affected with anti-Ma encephalitis and presenting with narcolepsy and cataplexy, along with the other spectrum features [14, 16] or in patients with GBS having hallucinations and RBD [13].

States of being instability also result in peculiar motor behaviors, due to the loss of the physiological inhibition of motor activity and of muscle tone that physiologically occurs during sleep.

Excessive muscle twitching and jerks, and RBD, are mainly seen in the context of intermittent/intermediate SD, as well as with autoimmune encephalitis and NT1, while "oneiric stupor" is the motor hallmark of *agrypnia excitata*.

The different motor patterns possibly reflect the different degree of states of being instability.

Indeed, while in the first case dissociated REM mainly comes into the form of RSWA (i.e., absence of muscle atonia, but other ways preserved descriptor of REM stage), in *agrypnia excitata*, EEG is an admixture of stage 1/REM sleep, and therefore the movements/behaviors may reflect this "undefined" status, merging mentation of NREM and REM sleep.

Conclusion

Even if lately it has been emphasized that sleep and wake are properties of small groups of neurons [52], usually they manifest as a whole phenomenon.

However, when central structures orchestrating state of being fail for different reasons and at different levels of the network, deviant pattern of states of being will be seen.

Everybody may experience a dissociation of states, especially at state transition, as, for example, when we experienced an illusion or a hallucination just

prior to falling asleep. What makes this often-normal condition a disorder is the frequency, duration, and degree of severity of such dissociation.

Dissociation of state disorders, such as RBD, cataplexy, hypnagogic hallucinations, etc., is more frequent in particular diseases and therefore may be a clue toward their correct diagnosis, such as for cataplexy, which is the motor hallmark of NT1, or may be a biomarker of other related conditions, such as RBD for alpha-synuclein-mediated diseases.

The extreme expression of state dissociation is SD, characterized by frequent state transitions and asynchronous and aberrant occurrence of features of different states of being as seen in pediatric NT1 or in autoimmune encephalitis, until reaching the maximum degree of severity in *agrypnia excitata*, where the brain is no longer able to produce a full-blown state of being (This topic is also discussed in Chap. 12 on Acute RBD).

Extensive video-polysomnography is mandatory in order to recognize all the above conditions, but currently the scoring can be only descriptive as the conventional scoring system lacks the labels for categorizing the neurophysiological and behavioral features of SD.

The pathological process underlying state dissociation more frequently involves structures located in the forebrain or brainstem, which are known to orchestrate sleep/wake regulation [49]. The network may be interrupted at different levels, giving rise to an imbalance in communication and synchronization between the neuronal structures involved.

Nowadays, the study of these conditions is partly hampered by the lack of a shared classifications of SD and by the absence of labels for state dissociation (as, e.g., we do not have a neurophysiological label in order to indicate conditions where elements of NREM and REM are present at the same time). Additional video-PSG documentations of different conditions associated with dissociation of states along with a consensus on SD classification/subtypes are therefore willing to that regard.

Note Added in Proof An additional case has recently been published: 1) Puligheddu M, Congiu P, Laccu I, et al. Overlap parasomnia disorder in a case of Creutzfeldt-Jakob disease. Sleep Med. 2017;36:75–7.

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Part IV

Clinical Research and Issues in RBD

Local Cortical Activations During REM Sleep and Implications for RBD

29

Paola Proserpio, Michele Terzaghi, and Lino Nobili

29.1 Introduction

REM sleep can be considered as a state of high cerebral and low physical activation. Indeed, subjects awakened from REM sleep may report florid and vivid story-like dreams [1]; in our dreams we move and act with different and complex motor behaviors, but actually we are completely motionless. Indeed, despite generalized postural muscle atonia, REM sleep is characterized by the presence of different markers of brain activation: EEG activity shows a "wake-like" pattern, brain metabolism increases in different cortical regions, and behaviorally signs of activations, such as rapid ocular movements and muscular twitches, appear.

However, from an electrophysiological point of view, there is a paucity of studies analyzing directly the activity of the human motor cortex during REM sleep. Animal models and clinical observations in patients with REM sleep behavior disorder (RBD) suggest a possible activation of the motor cortex during REM sleep. In particular, in RBD, muscle atonia is lost, and patients are deemed to enact their dreams with coordinated and often violent motor behaviors. As mentioned in Chaps. 40 and 44, the core circuits required for generating REM sleep are contained within the brainstem, with the involvement of other midbrain and forebrain circuits for their modulation. However, considering that during RBD, movements are often highly

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elaborated, resembling voluntary movements during wakefulness, it has been hypothesized that also the motor cortex could be involved in driving movement during RBD [2]. This theory is confirmed by the observation that pyramidal tract neurons, which mediate voluntary limb movement, are highly active during both wakefulness and REM sleep [3].

From a similar point of view, a clinical and video-polysomnography (vPSG) investigation of RBD in Parkinson's disease postulated that the restored motor control during REM sleep in this group of patients originates from the motor cortex and that the inputs generated follow the pyramidal tract, bypassing the basal ganglia [4].

REM sleep can be subdivided into two different sub-states, characterized by functionally different neuronal circuits and different responsiveness to external stimuli: phasic REM sleep (REM sleep with bursts of rapid ocular movements, REMs) and tonic REM sleep (REM sleep without REMs) [5, 6]. Compared to tonic REM sleep, phasic REM sleep is associated with activation in the right lateral geniculate body, the posterior hypothalamus, and the occipital cortex as demonstrated in earlier positron emission tomography (PET) studies [7]. A more recent functional MRI study with simultaneous PSG recordings while applying acoustic stimulation showed that within REM sleep a widespread thalamocortical synchronized activity is selectively enhanced during phasic REM sleep when compared with a predominantly tonic REM sleep background [8]. In addition, the authors observed a strongest decrease in brain reactivity to acoustic stimulation during phasic REM sleep periods, whereas processing of acoustic stimulation was preserved during tonic REM sleep as compared with wakefulness. These data seem to suggest that phasic REM sleep acts as a functionally isolated and closed intrinsic loop [8].

Evidence from clinical studies has shown that complex motor-behavioral episodes in RBD were significantly more likely to occur during phasic REM sleep than during tonic REM sleep [9, 10], suggesting a different level of activation of the motor cortex during these two REM sleep sub-states.

29.2 Activation of the Motor Cortex During REM Sleep

Previous studies, conducted with intracerebral electrodes, have shown that during NREM sleep, the motor cortex exhibits frequent activations (lasting from 5 to more than 60 s) characterized by an abrupt interruption of the sleep electroencephalographic (EEG) slow wave pattern and by the appearance of a wake-like EEG high-frequency pattern (alpha and/or beta rhythm). These local activations in the motor cortex could occur in absence of any movements and were paralleled by a concomitant increase of slow waves in the dorsolateral prefrontal cortex (dlPFc) and scalp EEG recordings [11, 12].

In recent work, De Carli et al. [13] evaluated the activity of the motor cortex during physiologic REM sleep. Particularly on the basis of the above-described clinical observations derived from RBD, the authors hypothesized that the electrophysiological activity of the motor cortex during phasic REM sleep could be similar to that occurring during voluntary movements. In order to verify this hypothesis, the activity of the motor cortex and the dlPFc in seven patients with drug-resistant epilepsy

undergoing presurgical evaluation with stereotactically implanted intracerebral electrodes (stereo-EEG, SEEG) was analyzed. The unequivocal localization of contacts pairs within the motor cortex (in particular within the paracentral lobule, leg motor area) and dlPFc was confirmed by post-implantation magnetic resonance imaging, intracerebral electrical stimulation, and evoked motor potentials [14]. DlPFc was selected as a "control" anatomical region because in a previous SEEG study, this brain structure showed a physiological and progressive decay of slow wave activity across NREM sleep cycles comparable to scalp sleep EEG dynamics [11]. Mean SEEG power spectrum of the motor cortex and dlPFc during phasic and tonic REM sleep as well as in voluntary movement during wakefulness was compared.

As shown in Fig. 29.1, during tonic REM sleep, motor cortex showed an alpha-like oscillatory activity (mu rhythm), which disappeared during phasic REM sleep, characterized by a desynchronized pattern. The results of this visual analysis were confirmed by the log-transformed power spectra of the relevant motor cortex EEG signals, showing a decrease of power in a large frequency band up to 25 Hz, with a slight increase of power above 25 Hz during phasic REM sleep.

Post hoc comparisons showed that only the motor cortex presented higher mean frequency spectral values during phasic REM sleep than during tonic REM sleep, while the difference was not significant in dlPFc (motor cortex phasic, 20.45 ± 0.73 Hz, vs. motor cortex tonic, 17.78 ± 0.47 Hz, $p < 0.002$; dlPFc phasic, 19.5 ± 60.40 Hz, vs. dlPFc tonic, 19.08 ± 0.46 Hz, NS; mean standard error).

In order to evaluate if the activation of the motor cortex could be directly related to the occurrence of REMs, mean frequency values associated with the 8-second intervals preceding and following the onset of REMs were analyzed, and no significant difference was found (motor cortex pre, 19.98 ± 0.86 Hz; motor cortex post, 20.89 ± 1.08 Hz; paired *t* test = 1.58, d*f* = 6, NS; mean standard error) (Fig. 29.2).

This suggests that the activation of the motor cortex is not related to REMs per se, but seems to reflect a widespread involvement of the motor system during this specific REM sleep sub-state (i.e., phasic REM sleep). This observation could also justify the occurrence of sporadic and brief RBD episodes unrelated to concomitant REMs.

In order to evaluate possible similarities between the EEG activity of the motor cortex during REM sleep and wakefulness, electrophysiological data were also acquired during the day following nocturnal sleep recordings. During the waking sessions, while patients were lying on their back in a resting condition (with closed eyes), they were requested to raise the leg corresponding to the motor area investigated with intracerebral electrodes. In Fig. 29.3, an EEG trace example of the activity of the motor cortex at rest and during voluntary leg movements in a single subject is represented. A predominance of a clear mu rhythm (8–12 Hz) characterizes the premovement epoch and disappears at movement onset, followed by a predominance of higher-frequency beta activity. Mean EEG spectra in the motor cortex showed a decrease of power in a large frequency band up to 25 Hz and with a slight increase of power above 25 Hz during leg movement. Mean frequency was significantly affected by the experimental condition (before or after movement onset, $p < 0.001$) and was not significantly different between regions (motor cortex vs. dlPFc, $F_{1,6} = 0.41$, NS), but the region-condition interaction was significant

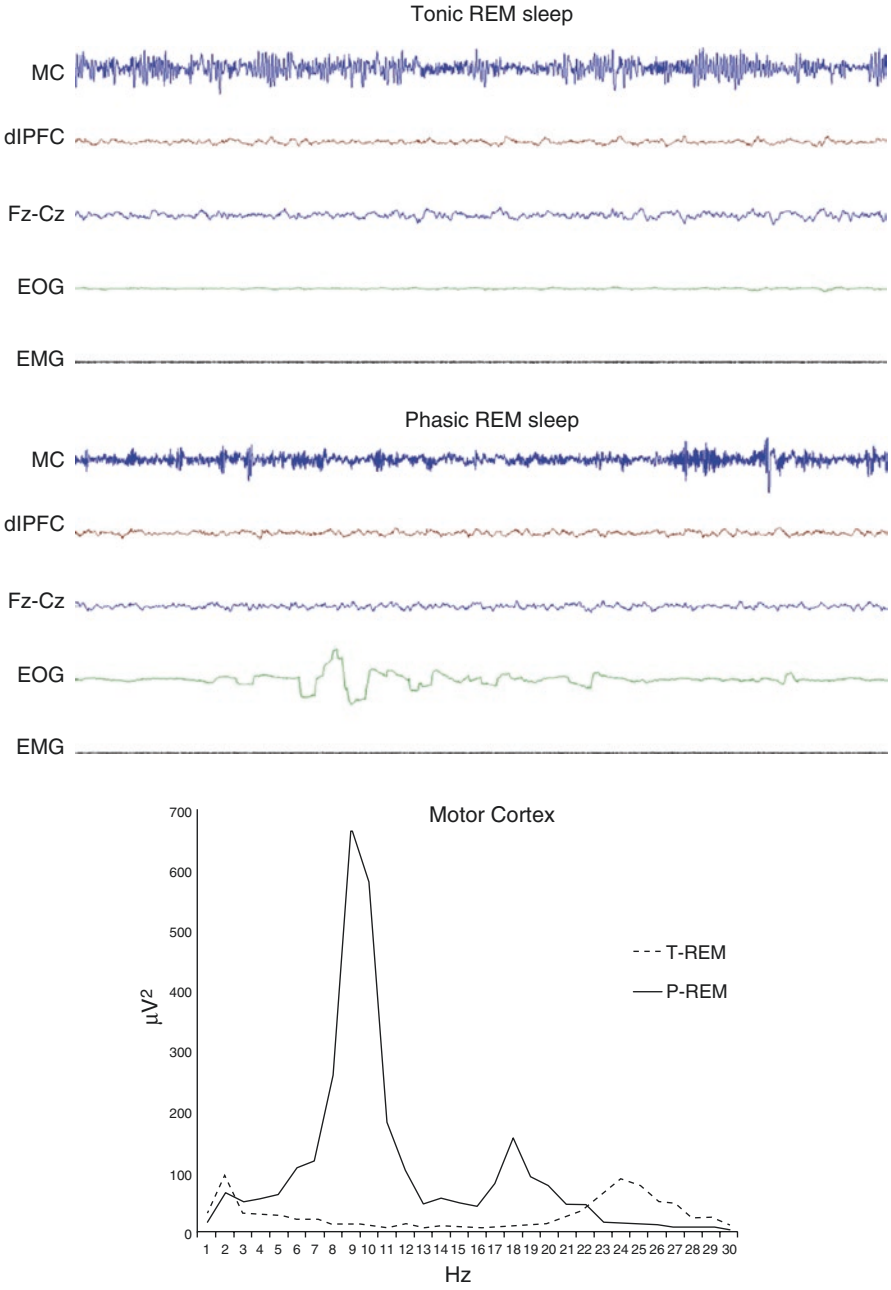

Fig. 29.1 Example of tonic and phasic rapid eye movement (REM) 30-second epochs. Each epoch shows three electroencephalographic (EEG) derivations (*MC* motor cortex, *dlPFC* dorsolateral prefrontal cortex, *FZ-CZ* scalp EEG), one electrooculographic (Eog) trace, and one chin electromyographic (Emg) trace. In the bottom part absolute values of motor cortex EEG spectra during tonic and phasic REM sleep are shown

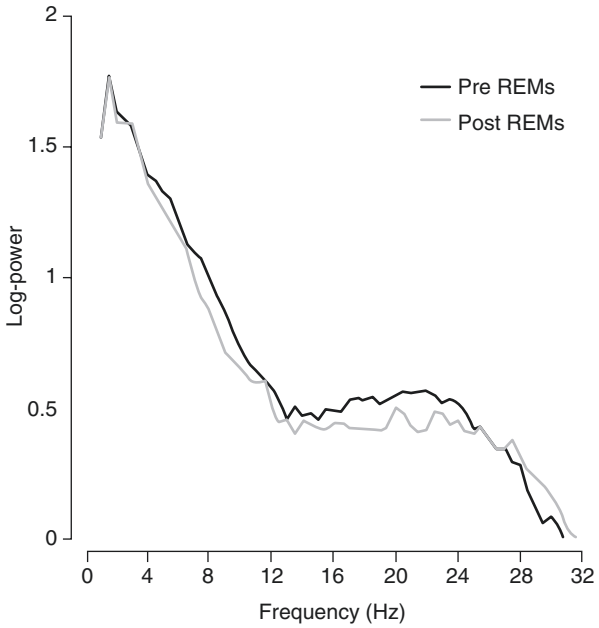

Fig. 29.2 Mean log-transformed power EEG spectra of motor cortex associated with the 8-second intervals preceding and following the onset of rapid eye movements (REMs)

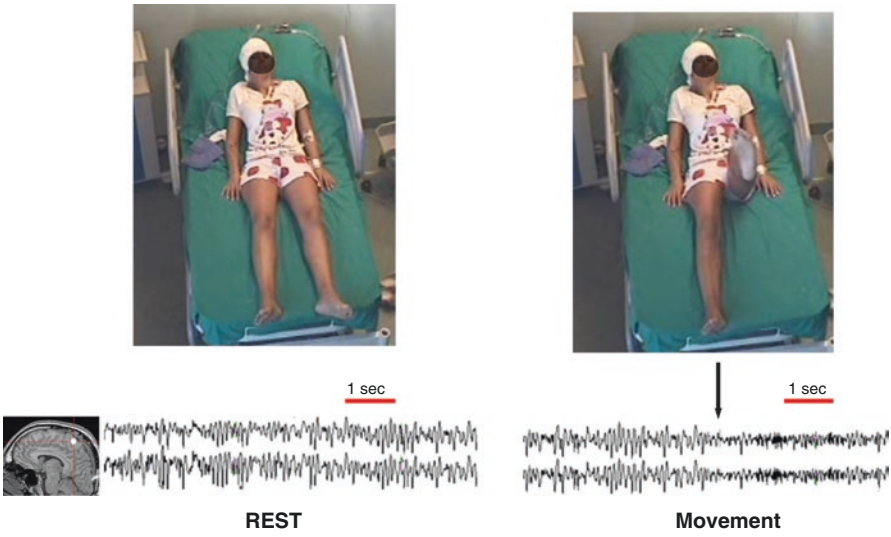

Fig. 29.3 Example of electroencephalographic (EEG) activity in the motor cortex (paracentral lobule; white circle in the sagittal magnetic resonance image) during rest and voluntary limb movement (arrow)

($F_{1,6}$ = 40.62, $p < 0.001$). Post hoc comparisons demonstrated that only the motor cortex presented significant changes between conditions (motor cortex after movement, 20.81 ± 0.87 Hz, vs. motor cortex before movement, 17.96 ± 0.81 Hz, $p < 0.001$; dlPFc after movement, 19.18 ± 0.78 Hz, vs. dlPFc before movement, 18.57 ± 0.55 Hz, NS; mean standard error). It's worth underlining that similar EEG frequency values and changes were observed in the motor cortex during wakefulness (before and after movement) and during phasic and tonic REM sleep. In particular, motor cortex showed a similar increase of the mean EEG frequency during phasic REM sleep and active wakefulness compared to tonic REM sleep and resting state, respectively (Table 29.1). These data suggest that during phasic REM sleep and active wakefulness, the motor cortex exhibits a similar pattern of activation.

Previous studies have already showed that the sensory-motor cortex of relaxed humans exhibits rhythmic activities around 10 and 20 Hz and such activity is suppressed during movement [15–17]. Intracerebral recording confirms these data, showing that this behavior seems to be specific to the primary cortex, and not involving other associative areas, such as the dlPFc. Analogously, in 2007 Miller et al. [18], using electrocorticography, quantified changes in electrocorticographic signals associated with motor movement in a group of epileptic patients with subdural electrode arrays placed for identification of seizure foci. They observed a spatially broad decrease in power in a low-frequency band (8–32 Hz), including the disappearance of the peak in the "mu rhythm" spectral frequency, and a spatially more focal increase in power in a broad high-frequency band (up to 100 Hz) during movement compared with rest. Moreover, they found that this high-frequency change seems to be particularly specific to the Rolandic cortex.

More recently, the same group demonstrated that this "activation" of the motor cortex is a phenomenon not only related to the movement but that can also be observed in other conditions, such as motor imagery [19]. In particular, they measured electrocorticographic cortical surface potentials during overt action and kinesthetic imagery of the same movement. As already described in MEG- and EEG-based imagery studies [20, 21], they found a similar pattern of desynchronization of the primary motor areas between movement and imagery [19].

Dreams characterized by actions seem to be more frequently reported by patients after an awakening from phasic REM sleep than from tonic REM sleep [22]; our observations seem to represent the electrophysiological background of these findings. It can be hypothesized that during dreamed movements the motor cortex can be activated, as observed during active wakefulness or during motor imagery. A

Table 29.1 Mean frequency spectral values of the motor cortex during rest, movement, tonic, and phasic REM sleep

Rest	*Tonic REM sleep*
17.96 ± 0.81 Hz	17.87±0.47 Hz
Movement	*Phasic REM sleep*
20.81 ± 0.87 Hz	20.45 ± 0.73 Hz

Notice a similar increase of the mean EEG frequency during phasic REM sleep and active wakefulness compared to tonic REM sleep and resting state, respectively

fMRI and near-infrared spectroscopy study in lucid dreamers seems to confirm this interpretation [23]. In lucid dreams, the subject is aware of the dreaming state and capable of performing predefined actions. By combining brain imaging with polysomnography, Dresler et al. [23] observed that a predefined motor task performed during dreaming elicits neuronal activation in the sensorimotor cortex that largely overlaps with the activation observed during motor execution or during motor imagery.

Elevated motor cortical activity associated with REM sleep has been already described in electrophysiological animal studies. In particular, using an autonomous, implantable recording system, Jackson et al. [24] examined the relationships between the firing of motor cortex cells and forearm muscle activity in the macaque monkey during active wakefulness and natural sleep. They found that during the night, motor cortex cells often exhibited regular periods of high firing rate, corresponding to periods of desynchronized EEG possibly related to REM episodes. Indeed, the highest firing rates were comparable to daytime values, but associated with complete atonia, characteristic of REM sleep. A more recent study conducted in freely behaving mice measured spectral properties and cross-frequency coupling of left parietal cortex activity during wakefulness and during the two REM sleep sub-states [25]. They found higher spectral frequencies and larger band power in phasic REM sleep compared to tonic REM sleep and wakefulness, suggesting similarities between phasic REM sleep and active waking.

In conclusion, SEEG findings in humans seem to confirm a similar pattern of activation of motor cortex in phasic REM sleep and active wakefulness as observed in animal studies. However, although SEEG offers a unique opportunity to investigate simultaneously the activity of different cortical and subcortical structures along the entire vigilance spectrum, going from active wakefulness to REM sleep and deep NREM sleep, this invasive technique does not allow the exploration of the entire brain structures in a single patient. SEEG data show a desynchronization of the EEG activity during active wakefulness and phasic REM sleep only in the motor cortex and not in the dlPFc. It can be hypothesized that this activation is a specific pattern belonging to primary brain areas and not to the associative ones. This hypothesis seems to be supported by functional studies demonstrating that during REM sleep, several brain regions (subserving important executive and attentional functions during wake) are significantly hypoactive when compared to wakefulness (i.e., the dlPFc, the orbitofrontal cortex, the posterior cingulate gyrus, and the precuneus) [26, 27].

29.3 Activation of the Limbic System During REM Sleep

Recent studies investigated the activity of other human brain structures during REM sleep, such as the limbic or the visual system. In particular, several studies have already shown that the human amygdala is activated selectively during REM sleep with respect to wakefulness and NREM sleep [28, 29]. More recent functional neuroimaging studies seem to demonstrate that the amygdala activation during this

sleep stage is related to the occurrence of REMs. Indeed, magnetoencephalographic current density in the amygdala increases several milliseconds before the onset of REMs in REM sleep [30]. More recently, simultaneous EEG and functional magnetic resonance imaging recordings found an increased amygdala activation in a close time relation to the REMs of REM sleep [8, 31]. In 2016, Corsi-Cabrera et al. [32] employed SEEG recording to analyze, with higher temporal and spatial resolutions, the activity of the amygdala during spontaneous sleep in four epileptic patients with depth electrodes implanted in the temporal lobes. They observed a transient activation of the amygdala time-locked to the onset of REMs during REM sleep, but not during waking eye movements. In particular, absolute power in the 44–48 Hz band increased significantly in the 250-ms time window after eye movement onset during REM sleep. The increase in gamma activity in the absence of known external visual input seems to suggest a transient amygdala activation related to an endogenous excitatory signal time-locked to REMs. This observation seems to be in line with electrophysiological studies in rats showing that REMs are time-locked to ponto-geniculo-occipital (PGO) waves, generated at the pontine level [33], and propagating not only to visual areas but also to other thalamic nuclei, the neocortex [34] and the amygdala [35]. From an electrophysiological point of view, transient activation of the amygdala during phasic REM sleep seems to suggest its central role for a further limbic-paralimbic network activation during this sleep sub-state. Finally, these findings suggest a participation of the amygdala in the emotional content of dreams, as well as for the reactivation and consolidation of emotional memories during REM sleep [32, 36, 37].

29.4 Activation of the Visual System During REM Sleep

Early positron emission tomography (PET) studies found that during REM sleep, activation within the temporo-occipital regions showed some functional dissociation: extrastriate visual cortices (particularly within the ventral processing stream) activation correlated with an unexpected striate cortex (primary visual cortex) deactivation during REM sleep [38]. For these authors, opposite interactions between low- and high-level visual areas during REM sleep might indicate that internal visual information is processed within a closed system (extrastriate areas and paralimbic projections, among others) dissociated from interactions with the environment (via striate cortex and prefrontal cortex, both deactivated during REM sleep; [38]). These early PET results are also consistent with the observation that patients with cortical blindness (after primary visual cortex or perichiasmatic lesions) report that they still dream with visual images [39].

More recently, some research has focused upon phasic activities of visual cortex temporally related to REMs during REM sleep. Peigneux et al. [7] showed a high positive correlation between REM density and visual cortex activities. By means of simultaneous fMRI and PSG recording during REM sleep, and event-related analysis time-locked to the occurrence of REMs, Miyauchi et al. [31] found an activation of the pontine tegmentum, ventroposterior thalamus, and primary visual cortex

before the onset of REMs. Due to the low temporal resolution of these neuroimaging techniques (PET and fMRI), some authors employed EEG/MEG recording to analyze the temporal relationship between REMs and brain activities, finding significant activities in the visual cortex before [30] or after [40] the REMs.

A more recent work employed intracerebral EEG recordings to establish the relation between the activity in visual-mnemonic regions and the REMS of REM sleep and to compare such modulations with those occurring during waking vision [41]. To this end, they examined the intracranial EEG and single-unit activities in the medial temporal lobe and neocortex surrounding REMs during sleep and wakefulness and during controlled visual stimulation in drug-resistant epileptic patients. They observed that REMs during sleep were associated with transient biphasic modulations of spiking activity in the mid temporal lobe, related to evoked potentials in depth EEG signals. In particular, individual neurons exhibit reduced firing rates before REMs, as well as transient increases in firing rate immediately after REMs, similar to activity patterns observed upon image presentation during fixation without eye movements. The authors assumed that these evoked potentials time-locked to REMs during REM sleep could be closely related to PGO potentials. Indeed, although PGO waves have been observed in cats, recent studies have already described similar phenomena in humans [7, 30, 31]. Moreover, initially PGO waves were believed to occur exclusively during sleep, but subsequent evidence suggested that they are analogous to visual evoked potentials [42]. The more convincing interpretation of these results seems to be that REMs during REM sleep transiently increase cortical excitability: the decreased activity before REMs may prepare the ground for subsequent processing by increasing sensitivity to inputs and amplifying responses, thus enhancing the signal-to-noise ratio. One of the main limitations of this study consists in the absence of electrodes examining directly the activity of the visual primary cortex.

Finally, a very recent work investigated the neural correlates of dreaming by performing serial awakenings of subjects recorded throughout the night with high-density EEG [43]. In both NREM and REM sleep, reports of dream experience were associated with local decreases in low-frequency activity in posterior cortical regions. Moreover, they found that specific contents of a subject's REM sleep dream—such as thoughts, perceptions, faces, places, movement, and speech—were associated with increased high-frequency EEG activity in specific cortical areas, which corresponded closely to those engaged during waking perception of the same contents.

29.5 Implications for RBD

Motor output and dream enactment are acknowledged as core distinctive features of RBD [44]. Yet, despite these hallmarks of RBD, neuropathophysiology of such dream-enactment events remains unclear. In this framework, investigating the cortical control of the motor and visual/emotional systems during REM sleep is expected to help clarify the cortical contributions to RBD clinical manifestations.

Motor activation in RBD manifests in the form of increased tonic and phasic muscle activity, exaggerated myoclonic twitching, limb movements (purposeful or aimless, violent or calm, rapid or slow), and complex motor-behavioral manifestations during REM sleep [9, 10, 45, 46]. The actual role of brainstem and cortical networks in generating movements and dream enactment has been discussed. In particular, some evidence suggests that the brainstem per se can play a crucial role in generating not only muscular twitches but also more complex movements, including defensive and aggressive behaviors [47]. On the contrary, complex elaborate movements reflecting socially learned behaviors were suggested to correspond to motor cortex activation [45]. Interestingly, the electrical stimulation of cingulate gyrus is reported to trigger movements similar to those commonly seen in RBD episodes [48].

Based on current possible interpretations of the potential brainstem role in movement generation in RBD, a dichotomous conceptualization can be formulated:

1. A bottom-up (brainstem-centric) hypothesis, identifying the brainstem as the main site responsible for generating movements (including complex behaviors). Accordingly, the brainstem would be the source of the pathological movements, while sensory feedback inputs to cortical networks would affect dream mentation [47].
2. A top-down (cortico-centric) hypothesis, postulating that cortical networks are the main site responsible for motor output related to dream mentation [45], with a permissive involvement of the brainstem.

Neuroimaging studies have revealed different patterns of activations during RBD episodes. In particular, by means of single-photon emission computed tomography (SPECT) and PSG recording, a selectively increased perfusion of the supplementary motor area was observed during a RBD episode [49]. Using the same technique in four patients with different RBD etiologies [50], all the RBD episodes were characterized by activations in the bilateral premotor areas, the interhemispheric cleft, the periaqueductal area, the dorsal and ventral pons, and the anterior lobe of the cerebellum. Moreover, this study also showed that the neural activity generating movements during RBD bypasses the basal ganglia, a mechanism that is shared by RBD patients with different etiologies. In line with this observation, complex, non-stereotyped motor manifestations during RBD episodes are observed in Parkinson's disease-affected subjects, suggesting that RBD motor activity could be generated by the motor cortex bypassing the basal ganglia, as a fundamental phenomenon in RBD, irrespective of the clinical subtype of RBD (idiopathic, secondary to Parkinson's disease, narcolepsy, etc.) [4].

In conclusion, the above-described findings in RBD patients and the occurrence of more complex RBD episodes during phasic REM sleep, together with the observation of activations of the motor, visual, and limbic systems during physiologic phasic REM sleep, seem to indicate a high level of sensory-motor drive during RBD episodes.

29.6 What Do These Data Add to the Interpretation of Motor Dyscontrol in RBD?

RBD patients show quite a wide variety of motor-behavioral manifestations. These range from simple, primitive movements to more complex movements (gestures, actions) occurring in isolation or in the context of what appears to be, in most cases, the enactment of a dream. Though RBD is primarily characterized by violent behaviors, nonviolent behaviors also occur, as well as facial and verbal mimicry not related to anger or aggression. This variability of the motor patterns may be an indication that different parts of the central motor system are involved in the genesis of movements in RBD. The observation that local activations and variations in cortical background rhythms occur in REM sleep argue in favor of a role of the cortical motor areas in the genesis of RBD manifestations.

However, it does not necessarily mean that cortical networks play the main role in RBD. Indeed, it can be hypothesized in an articulated model that takes into account both cortical networks and brainstem motor regulators, that these different components of the motor system are dynamically engaged to varying extents, resulting in a spectrum of muscular twitching, simple movements, complex movements, and aggressive and violent behaviors emerging as dream-enacting behaviors.

Future research agenda using stereo-EEG recordings, focusing on local cortical activity during phasic and tonic REM sleep, may include:

- Study of muscle activity (twitches, jerks, and more complex movements) synchronously with corresponding neural sensory and motor cortices
- Simultaneous analysis (when possible) of data from premotor, SMA, and primary motor cortices
- Analysis of data from visual regions specialized for different functions: dorsal and ventral stream

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Brain Imaging in RBD

30

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30.1 Introduction

Neuroimaging studies can provide in vivo insights to the early structural and functional brain changes in patients with idiopathic Rapid Eye Movement Sleep Behavior Disorder (iRBD). Ideally, neuroimaging measures should be able to (1) confirm the presence or absence of a specific latent α-synucleinopathy (be it Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), or Multiple System Atrophy (MSA)) in an individual with iRBD; (2) provide an estimation of the time to overt clinical manifestation of motor and/or cognitive symptoms; and (3) allow evaluation of the rate of disease progression. Although to date such a neuroimaging measure is not yet available, several neuroimaging modalities, combined with the appropriate analytical tools, appear to be promising. This chapter summarizes the major findings of neuroimaging studies in RBD. Molecular imaging techniques, magnetic resonance imaging (MRI), and transcranial sonography (TCS) are all discussed.

30.2 Structural Imaging Studies

30.2.1 Conventional Structural MRI

Early studies on structural alterations in the brains of iRBD patients revealed non-specific changes such as multifocal pontine lesions [1], white matter lesions [2, 3], ventricular enlargement [4], and atrophy [3, 5, 6]. However, the specificity of these findings is limited, as they commonly occur during aging [7].

Hippocampal and parahippocampal density was shown to be increased in one voxel-based morphometry (VBM) study [8], whereas another VBM study found reduced grey matter in the left parahippocampal gyrus of RBD patients (20 RBD patients, 18 controls [9]). The latter study also reported bilateral atrophy of the anterior lobes of the cerebellum and the tegmental portion of the pons [9]. Yet other VBM analyses revealed volume loss around the right superior frontal sulcus [5] and bilateral putamina of RBD patients [10]. Interestingly, putaminal volume was also reduced in RBD compared to early-stage PD in the latter study. Given that putaminal atrophy is typically observed in MSA [11–14], putaminal volume reduction in RBD may also indicate emerging MSA pathology. However, taking into account the rather low incidence of MSA, it does not seem likely that all of these patients will subsequently develop MSA and none PD.

Recently, neuromelanin-sensitive T1-weighted images were used to study the integrity of the locus coeruleus/subcoeruleus complex in RBD [15]. Reduced signal intensity was identified in the locus coeruleus/subcoeruleus complex of 21 RBD patients compared to 21 age- and gender-matched controls. Signal intensity correlated negatively with the proportion of REM sleep without atonia in the entire group (RBD and controls), but not with other sleep measures, and not within the patient group. Neuromelanin-sensitive imaging may provide an early marker of non-dopaminergic α-synucleinopathy which can be detected on an individual basis. Overall, the findings from structural MRI are still highly inconclusive, and it has yet to prove its usefulness for detecting disease-specific changes and monitoring disease progression (see Table 30.1).

Table 30.1 Magnetic resonance imaging in iRBD

	Study sample *n* (*n*♂; age in years ± SD; iRBD disease duration in years ± SD)		HC/iRBD/PD overall		iRBD vs. HC/young HC left/right		iRBD vs. PD/early PD left/right	
Conventional structural magnetic resonance imaging								
Culebras et al. [1]	iRBD 6	(4♂; range: 64–74; N/A)	*iRBD*: • Multifocal lesions in periventricular ($n = 5$) and dorsal pontomesencephalic areas ($n = 3$)		N/A		N/A	
Eisensehr et al. [3]	siRBD 8 iRBD 8 HC 11	(6♂; 62.3 ± 13.5; N/A) (7♂; 69.2 ± 7.6; N/A) (9♂; 61.6 ± 8.2)	*White matter lesions*:		N/A		N/A	
			HC: iRBD:	**27%** **25%**				
Ehrminger et al. [15]	iRBD 21 HC 21	(15♂; 67.4 ± 7.6; N/A) (17♂; 67.6 ± 6.3)			*Quantitative neuromelanin-sensitive imaging*: coeruleus/subcoeruleus complex ↓		N/A	
Ellmore et al. [10]	iRBD 5 Early PD 5 HC 7 Young HC 10	(4♂; 52.6 ± 10.1; N/A) (4♂; 60.0 ± 9.6) (4♂; 54.0 ± 7.8) (5♂; 26.3 ± 2.8)	*iRBD*: • Negative correlation between whole-brain volume and age • Positive correlation of quality of life with normalized putamen volumes and of performance on timed gait task with normalized nucleus caudatus and putamen volumes		Whole-brain volume:	↔	Whole-brain volume:	↔
					Nucleus caudatus volume:	↔/↔	Nucleus caudatus volume:	↔/↔
					Putaminal volume:	↓/↓	Putaminal volume:	↑/↔

(continued)

Table 30.1 (continued)

	Study sample *n* (*n*♂; age in years ± SD; iRBD disease duration in years ± SD)		HC/iRBD/PD overall		iRBD vs. HC/young HC left/right		iRBD vs. PD/early PD left/right
Hanyu et al. [9]	iRBD 20 HC 18	(17♂; 68 ± 7; 6 ± 5) (9♂; 71 ± 8)	N/A		Cerebellar volume (anterior lobes): Pontine volume (tegmental portion): Parahippocampal volume:	↓/↓ ↓ ↓/↔	N/A
Lee et al. [4]	iRBD 15 HC 20	(10♂; 62.8 ± 7.4; N/A) (12♂; 60 ± 6.4)	N/A		Gray/white matter volumes: Lateral ventricle volumes:	↔ ↑	N/A
Mazza et al. [3]	iRBD 8 HC 9	(7♂; 69.9 ± 8.2; 7.5 ± 4.8) (N/A; 67.4 ± 6.8)	*Single white matter lacunes/mild cortical atrophy*: HC: iRBD:	 **33%** **50%**	N/A		N/A
Rahayel et al. [5]	iRBD 24 HC 42	(20♂; 64.2 ± 7; 9.3 ± 9) (28♂; 63.3 ± 7.1)	*iRBD*: • No correlation between cortical thickness and UPDRS-III score/iRBD duration		*Corticometry*: Mean global cortical thickness: Medial frontal lobe/dorsolateral superior frontal gyrus/lingual gyrus/fusiform gyrus: *Voxel-based morphometry*: Volume around superior frontal sulcus:	 ↓ ↔/↓ ↔/↓	N/A

Shirakawa et al. [6]	iRBD 20 HC 7	(21♂; 63.4 ± 8.5; N/A) (7♂; 77.4 ± 4.2)	*Frontal lobe atrophy* HC: iRBD:	 **71%** **45%**	N/A	N/A
Diffusion tensor imaging						
Rahayel et al. [5]	iRBD 24 HC 42	(20♂; 64.2 ± 7; 9.3 ± 9) (28♂; 63.3 ± 7.1)	N/A		Mean diffusivity/axial diffusivity/fractional anisotropy/radial diffusivity:	↔	N/A
Scherfler et al. [8]	iRBD 26 HC 14	(21♂; 67.4 ± 4.9; 9.2 ± 6.4) (10♂; 64.5 ± 5.2)	N/A		*Mean diffusivity*: Mesencephalic/pontine tegmentum/formation reticularis: *Fractional anisotropy*: Mesencephalic tegmentum:	 ↑ ↓	N/A
Unger et al. [17]	iRBD 12 HC 12	(11♂; 59 ± 10.5; N/A) (3♂; 56.8 ± 10.6; N/A)	N/A		*Fractional anisotropy*: Fornix: White visual stream: Superior temporal lobe:	 ↓ ↓ ↓/↔	N/A

(continued)

Table 30.1 (continued)

	Study sample *n* (*n*♂; age in years ± SD; iRBD disease duration in years ± SD)		HC/iRBD/PD overall	iRBD vs. HC/young HC left/right		iRBD vs. PD/early PD left/right	
Resting-state functional magnetic resonance imaging							
Rolinski et al. [105]	iRBD 26 HC 23 PD 48	(22♂; 67 ± 7.7; 2.4 ± 2.1) (N/A) (31♂; 67 ± 7.7; 1.8 ± 1.5)		*Basal ganglia network activity*:		N/A	
				Putamen L	↓		
				Frontal (L,R), middle (R) orbital cortex	↓		
				Cingulate cortex (R)	↓		
				Middle temporal gyrus (L)	↓		
Ellmore et al. [104]	iRBD 10 HC 10 PD 11	(6♂; 57 ± 2.7; N/A) (4♂; 57 ± 2.4) (7♂; 62 ± 2.5)	N/A	*Cluster correlations*:		*Cluster correlations*:	
				Putamen-SN:	↓/↔	Putamen-SN:	↑/↔
				Cuneus/precuneus/ Brodmann area 7-SN:	↔/↑	Cuneus/ precuneus/ Brodmann area 7-SN:	↔/↑
				Superior occipital gyrus:	↔/↑	Superior occipital gyrus:	↔/↓
Susceptibility-weighted imaging							
De Marzi et al. [20]	iRBD 15 HC 42 PD 104	(13♂; 68 ± 10.0; N/A) (71♂; 61 ± 9.1) (16♂; 67 ± 9.2)	N/A	*Susceptibility-weighted imaging*:		N/A	
				Dorsolateral nigral hyperintensity in 2/3	↓		

Magnetic resonance imaging of iron deposition						
Lee et al. [4]	iRBD 15 HC 20	(10♂; 62.8 ± 7.4; N/A) (12♂; 60 ± 6.4)	N/A	Transverse relaxation rate (R2*):	↔/↔	N/A
Magnetic resonance spectroscopy						
Iranzo et al.[27]	iRBD 15 HC 15	(15♂; 65.7 ± 6.4; 5.2 ± 3) (15♂; 64.3 ± 7.1)	N/A	*N-Acetylaspartate/ creatine, choline/creatine, and myoinositol/creatine ratios*:		N/A
				Mesencephalon/pons:	↔	

Note: *HC* healthy controls, *N/A* not available/not applicable, *PD* Parkinson's disease, *(i)RBD* (idiopathic) rapid eye movement sleep behavior disorder, *siRBD* subclinical idiopathic RBD, *SN* substantia nigra, *UPDRS-III* unified Parkinson's disease rating scale, ♂ male, numbers indicate mean ± standard deviation

30.2.2 Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) allows assessment of the microstructural integrity of the brain by quantification of diffusion-driven displacement of water molecules. It has been used extensively to study microstructural alterations in PD and atypical parkinsonisms and has shown potential for early disease detection and in differential diagnosis [16]. However, only a few studies have employed DTI in RBD, and the findings so far have been heterogeneous.

Increased mean diffusivity (average magnitude of molecular displacement), reduced fractional anisotropy (directionality of local tract structure), and axial diffusivity (magnitude of molecular displacement parallel to axonal tracts) have been reported for different brainstem regions [8, 17], pointing to the pivotal role of microstructural brainstem damage in RBD pathophysiology [18, 19]. Additionally, altered substantia nigra (SN) fractional anisotropy was observed [17]. This finding has also been reported in several studies on PD [21] and may indicate an imminent neurodegenerative process. However, another DTI study did not detect any differences between RBD patients and controls [5].

Taken together, DTI provides some evidence for a pathophysiological overlap between RBD and PD. However, currently the findings are ambiguous, and the utility of DTI in monitoring RBD progression must be evaluated further.

30.2.3 Susceptibility-Weighted Imaging (SWI)

Recently, dorsolateral nigral hyperintensity (DNH) was assessed using high-field susceptibility-weighted imaging (SWI), a novel magnetic resonance imaging marker for PD. De Marzi and colleagues performed SWI sequences in 15 RBD subjects, 104 PD patients, and 42 healthy controls [20]. They found loss of DNH in more than three-fourths of RBD subjects (77%), which approaches the rate observed in PD (92%) and contrasts to findings in controls. Frosini and colleagues evaluated the SN on 7-Tesla SWI sequences. An abnormal SN signal was found in 1/14 healthy controls (7%), 9/15 iRBD patients (60%), and 27/28 PD patients (96%). All iRBD patients also underwent dopaminergic imaging with DAT-SPECT (see Sect. 30.3). Of the iRBD patients with nigrostriatal dysfunction on DAT-SPECT, 89% showed involvement of the SN on SWI. These findings indicate that SN involvement may be used to differentiate patients according to their prodromal stage [21]. However, further studies in larger and more diverse prodromal cohorts with longitudinal follow-up are needed to further substantiate this claim.

30.2.4 Magnetic Resonance Spectroscopy (MRS)

MR spectroscopy (MRS) allows for in vivo investigations to determine the presence and concentration of various tissue metabolites [22]. In humans, proton MRS (^{1}H-MRS) can be applied to monitor brain metabolism [23]. It has been employed in

several studies of MSA [24], PD [25], and dementia [26], giving valuable insight to disease pathogenesis. However, there is only one relevant study on MRS in RBD, which did not find any significant alterations of metabolic ratios in the midbrain or brainstem of patients compared to controls [27]. Therefore, no firm conclusions can be drawn regarding the usefulness of MRS in assessing RBD pathology and/or progression at this time.

30.2.5 MRI R2* Relaxometry for Measuring Iron Deposition

Increased brain iron deposition has been proposed to contribute to the formation of free radicals leading to oxidative damage and cell death, and has consequently been associated with human neurodegenerative processes [28]. While increased nigral iron content measured by a multiple-gradient echo sequence designed for rapid single-scan mapping of the proton transverse relaxation rate (R2*) has been reported in PD, data on iron deposition in MSA and DLB are not sufficient to draw general conclusions [29]. As for RBD, the only existing study using transverse relaxation rate (R2*) on a 3T MRI failed to demonstrate alterations of iron deposition in 15 patients as compared to 20 controls [4]. These results may either originate from insufficient power of the data, too-small effects to adjust for possible confounding variables, or alternatively, they may be representative of an RBD cohort which has not yet begun to phenoconvert. However, longitudinal studies are required to further explore a possible association of brain iron deposition and RBD progression. To date, the limited data in RBD allows no clear recommendation for use of this modality.

30.2.6 Combined Structural MRI Biomarkers

A recent study combined DTI measures, neuromelanin-sensitive mapping, and iron imaging (R2* increase) of the substantia nigra (SN) in order to discriminate between RBD patients (n = 19) and controls (n = 18) [30]. Patients with RBD showed a reduction in the neuromelanin-sensitive volume, signal intensity, and a decrease in fractional anisotropy versus controls; however, they showed no differences in R2* or axial, radial, or mean diffusivity. The three imaging measures (NM-sensitive volume, signal intensity, and fractional anisotropy) had a combined accuracy of 0.92. This combination of routinely-available structural MRI measurements of SN damage may provide a valuable compound imaging marker for the early detection of premotor PD.

30.2.7 Transcranial Sonography (TCS)

Increased iron deposition may also account for the SN hyperechogenicity detected in the majority of PD patients by Transcranial B-mode Sonography (TCS), also

known as Brain Parenchyma Sonography (BPS) [31]. In contrast, MSA and Progressive Supranuclear Palsy (PSP) patients are more likely to present with lenticular nucleus hyperechogenicity—however, this may be due to increased deposition of trace metals other than iron. Several studies have demonstrated that it may be possible to use TCS to differentiate between various parkinsonian disorders [32–34].

SN hyperechogenicity may also be a relevant tool for imaging parkinsonian disorders in the premotor phase. SN hyperechogenicity in the elderly has been linked to a 17.4-fold increased risk for developing PD within 3 years [31]. In addition, asymptomatic *PARK8* gene mutation carriers had a greater rate of SN hyperechogenicity compared with first-degree non-carrier relatives of PD patients and controls (58.3% versus 25% and 12.5%, respectively), but less than patients with idiopathic PD or PD *PARK8*-affected patients (87.5% and 75%). SN hyperechogenicity in asymptomatic carriers was also correlated with abnormal DAT-SPECT scans and presence of RBD [35].

Iranzo et al. investigated SN echogenicity and DAT-binding (see Sect. 30.3.1) in 43 iRBD patients. SN hyperechogenicity was found in 14 (36%) of the 39 RBD patients on whom TCS could adequately be performed, a rate more than three times higher than in age and gender-matched healthy controls. Upon 2.5-year follow-up, 8 (19%) of the original 43 iRBD patients had developed a neurodegenerative disease (PD, DLB, or MSA), and 5 (63%) of these exhibited SN hyperechogenicity, while none of the patients or controls with normal imaging findings had phenoconverted [36].

However, TCS may be a better marker for *predisposition* to neurodegenerative disease as opposed to a progression marker for determining rate of phenoconversion. At least one study has shown no growth in SN hyperechogenic areas of PD patients over the course of 5 years [37], and another study could not correlate SN hyperechogenicity to current age, duration of PD, or disease severity [34, 38].

Additionally, although TCS may be a fast, cheap, and radiation-free way of assessing predisposition to neurodegenerative disease, it does have some important limitations. As with all ultrasound-based technology, results are particularly operator dependent, and patients must have adequate temporal bone windows (one study could not perform TCS in 10% of RBD patients due to insufficient temporal bone windows [36]). Additionally, 10% of healthy controls were found to have SN hyperechogenicity as well, so relevant clinical support for an adequate diagnosis is necessary [39].

30.3 Imaging of the Dopaminergic System

Molecular imaging techniques such as positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) can be used to study specific aspects of brain structure and function, depending on the employed radiopharmaceutical tracer. Several PET and SPECT radiotracers are available to study the dopaminergic system, and each tracer targets different aspects of the dopaminergic

nerve terminal (Fig. 30.1). Both PD and DLB have been associated with a decrease in the density of dopamine transporter protein (DAT) located on the pre- and postsynaptic plasma membranes of nigrostriatal dopaminergic neurons [40, 41]. This can be seen in MSA as well [42]. FDOPA-PET and [^{123}I]FP-CIT-SPECT (also known as DAT-SPECT) are two commonly used presynaptic dopaminergic imaging

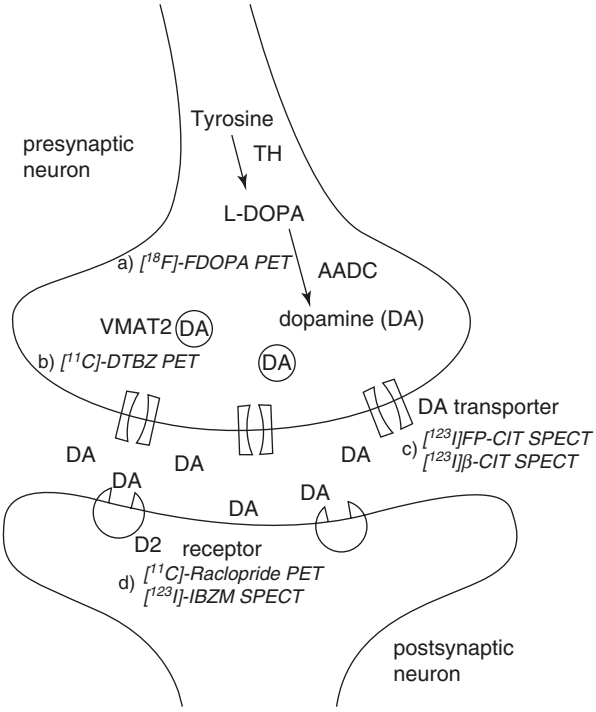

Fig. 30.1 Schematic representation of dopamine (DA) synthesis within dopaminergic neurons, including sites of action of dopaminergic tracers (a, b, c, d). DA is synthesized within the striatal nerve terminals of dopaminergic neurons. Within dopaminergic terminal cytoplasm, the enzyme tyrosine hydroxylase (TH) first converts tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA). Aromatic amino acid decarboxylase (AADC) then decarboxylates L-DOPA to DA. The vesicular monoamine transporter type 2 (VMAT 2) then allows the synthesized DA to enter the presynaptic vesicles. Following depolarization of nerve terminals, the stored DA is released into the synaptic cleft and interacts with pre- and postsynaptic DA receptors. **a**) The PET tracer [^{18}F]FDOPA binds to AADC and estimates the rate of decarboxylation of FDOPA to [^{18}F]fluorodopamine, which represents a function of striatal levodopa decarboxylase activity; **b**) the PET tracer [^{11}C]DTBZ binds to VMAT2 and blocks the uptake of monoamines into the vesicles, which represents the integrity of striatal monoaminergic nerve terminal density; **c**) The SPECT tracers [^{123}I]FP-CIT and [^{123}I]β-CIT bind to the DA transporter, which represents a marker of the integrity of presynaptic nigrostriatal dopamine terminals; **d**) The PET tracer [^{11}C]raclopride and the SPECT tracer [^{123}I] iodobenzamide (IBZM) bind to the postsynaptic dopamine D2 receptor, which allows for the visualization of striatal dopamine D2 receptor-binding. From Teune/Leenders [154]

techniques. FDOPA is a fluorinated analogue of L-DOPA, the direct precursor to dopamine, and corresponds to striatal dopamine production; while [^{123}I]FP-CIT, an isotope of iodine, has a high affinity for DATs. The uptake of these tracers is highly correlated to one another [43].

In addition to the presynaptic damage seen in PD and DLB, there is also an early decrease of nigrostriatal postsynaptic D2 receptors in MSA (which, by contrast, are often compensatorily upregulated in the beginning stages of PD) [44]. As presynaptic dopaminergic imaging is unable to distinguish between PD and MSA, [^{11}C] raclopride-PET and [^{123}I]iodobenzamine (IBZM)-SPECT imaging are used for identifying postsynaptic neuronal damage in MSA; raclopride, and IBZM are both selective D2 receptor antagonists.

30.3.1 Presynaptic Dopaminergic Imaging

In patients with early PD, uptake of presynaptic dopaminergic tracers is typically diminished in the posterior putamen, contralateral to the more severely affected side of the body [45]. Both FDOPA uptake and DAT-binding can be used to assess the rate of disease progression in PD; for instance, increased severity of parkinsonian motor symptoms tends to correlate proportionally to decreased FDOPA uptake [46].

Based on data from DAT-imaging and pathological studies, it is estimated that on average, there are more than 5 years from the onset of nigral dopaminergic neuronal damage to the first appearance of clinical parkinsonism, by which time roughly half of the SN cells are already lost [47]. Consequently, it is no surprise that reduced radiotracer uptake is often evident years before emergence of clinical parkinsonism [48].

For instance, one study followed 80 asymptomatic Ashkenazi Jewish carriers of the G2019S mutation in the *LRRK2 (PARK8)* gene, the most common genetic mutation linked to increased PD risk worldwide. It was determined that while PD patients had significantly lower striatal DAT-binding than both asymptomatic carriers and healthy controls, carriers of the *PARK8* mutation had lower DAT-binding than controls—particularly in the dorsal striatum, a region often known to be affected earliest in PD. Within 2 years of DAT-SPECT imaging, 3 carriers (4%) had phenoconverted to PD, with decreased DAT-binding seen in 2 of them. However, as penetrance of the mutation is variable, it is still unclear how many of these carriers will ultimately convert to PD [49].

In iRBD, early presynaptic dopaminergic tracer studies have confirmed deficits in the striatal binding of iRBD patients compared to age- and gender-matched controls [50, 51]. This was further supported in larger cohorts, demonstrating that 20–40% of iRBD patients have abnormal DAT-SPECT scans [36, 52, 53].

The reduction in striatal DAT-binding in iRBD (7–8% reduced compared to normal) is less severe than in PD (20–50%) [36, 54]. This may indicate that DAT-binding has potential as a progression marker. In support of this, subtle motor deficits were shown to be predictive of a DAT deficit in iRBD [55]. In contrast, hyposmia is not obviously related to DAT-binding [51, 55, 56].

Table 30.2 Neuroinflammation imaging in iRBD

	Study sample *n* (*n*♂; average age in years ± SD; average disease duration in months)		Tracer/ imaging	Main takeaway	Additional
Microglial activation imaging					
Stokholm et al. [58]	HC 19 iRBD 20	(19♂; 65.2 ± 4.0; N/A) (17♂; 66.6 ± 6.3; 46)	[^{11}C] PK11195-PET	*Striatal [^{11}C] PK11195-binding*: iRBD > HC, particularly in the left SN • 7/20 (35%) iRBD patients had abnormally raised SN [^{11}C]PK11195 uptake, all of whom also had abnormally decreased [^{18}F]FDOPA uptake in the ipsilateral putamen • 2/20 (10%) iRBD patients had abnormally raised [^{11}C]PK11195 uptake in the putamen, 2/20 (10%) had abnormally raised uptake in the caudate, and 1/20 (5%) had bilateral abnormal binding in the SN, putamen, and caudate	Increased [^{11}C] PK11195 uptake in the left SN was correlated with reduced [^{18}F] FDOPA uptake in the ipsilateral caudate *(See Sect. on Presynaptic dopaminergic imaging for more on this article)*

Note: *HC* healthy controls, *N/A* not available/not applicable, *PD* Parkinson's disease, *(i)RBD* (idiopathic) rapid eye movement sleep behavior disorder, *SN* substantia nigra, *UPDRS-III* unified Parkinson's disease rating scale, ♂ male, numbers indicate mean ± standard deviation

Interestingly, a recent study found an association between the presence of phosphorylated α-synuclein deposits in dermal nerve fibers and decreased [^{123}I]FP-CIT uptake in iRBD patients (n = 18) and PD patients (n = 25). Meanwhile, controls (n = 20) in which [^{123}I]FP-CIT uptake was not measured and assumed to be normal did not have dermal phospho-α-synuclein deposits [57]. Another recent interesting study found a connection between increased microglial activation in the left SN, as measured by increased [^{11}C]PK11195 uptake on PET imaging, to reduced bilateral putaminal [^{18}F]FDOPA uptake in iRBD patients (n = 20) as compared to controls (n = 19) (see Table 30.2) [58].

There have been three large longitudinal DAT-binding studies in iRBD. In the first, baseline DAT-SPECT findings were compared to final clinical diagnosis after 2.5 years of follow-up in 43 iRBD patients. At baseline, 17 iRBD patients (40%) had reduced striatal [^{123}I]FP-CIT uptake. Of all of the iRBD patients, 8 patients were

eventually diagnosed with a neurodegenerative disease (5 to PD, 2 to DLB, and 1 to MSA). Of these phenoconverters, 6 (75%) had abnormal DAT-binding at baseline. However, 2 iRBD patients with normal DAT-SPECT scans also converted (1 to PD and 1 to DLB) [36].

A second serial [^{123}I]FP-CIT-SPECT imaging study (at baseline, 1.5, and 3 years of follow-up) reported an average DAT-binding rate of decline of 6% per year in iRBD patients (n = 20), compared with 3% in controls (n = 20). At baseline, 10 iRBD patients presented with abnormal [^{123}I]FP-CIT uptake; after 3 years, 13 patients had abnormal uptake. Additionally, by the 3-year mark, the 3 patients with the lowest baseline [^{123}I]FP-CIT uptake had converted to PD. The rate of decline in DAT-binding was 10% per year in these 3 subjects [47]. These findings indicate that the rate of decline in [^{123}I]FP-CIT uptake may correspond to likelihood of imminent phenoconversion.

The third major [^{123}I]FP-CIT-SPECT imaging study of 87 iRBD patients found that at baseline, DAT-binding deficits were seen in 51 patients (59%). Of these, 25 (49%) developed α-synucleinopathies over the course of clinical follow-up, which averaged approximately 6 years (11 converted to PD, 13 to DLB, and 1 to MSA). iRBD patients with abnormal [^{123}I]FP-CIT uptake showed increased risk of imminent phenoconversion compared to those with normal uptake (20% versus 6% at 3-year follow-up, 33% versus 18% at 5-year follow-up). Additionally, it was found that among patients with abnormal [^{123}I]FP-CIT uptake, those with significant reduction in putaminal DAT-binding (greater than 25%) could differentiate iRBD patients who phenoconverted after 3 years of follow-up from those who did not [59].

A recent systematic review evaluated the results of 16 presynaptic dopaminergic imaging studies in iRBD patients [60]. As these studies were technically and clinically heterogeneous, data from each study was mathematically transformed to allow comparison. It was shown that tracer uptake in the putamen decreased progressively from healthy controls to iRBD, PD, and eventually PD patients with concurrent RBD. Although tracer uptake in the caudate was significantly lower in iRBD patients compared to controls, caudate uptake largely overlapped between iRBD and PD patients. Thus, the degree of nigro-caudate dopaminergic impairment in iRBD is similar to that in established PD. The authors note that the transformation of data could have influenced results and encourage efforts in harmonizing protocols for presynaptic dopaminergic imaging (see Table 30.3).

It appears that presynaptic dopaminergic imaging is a valid tool for monitoring disease progression and identifying those at greatest risk for phenoconversion. However, it must be noted that uptake abnormalities are not always present, or do not always correlate to apparent disease severity even after clinical manifestation of α-synucleinopathy. One study found that upon performing DAT-SPECT imaging on 67 probable symptomatic DLB patients, 7 (10%) had negative scans. Two of these patients were lost to follow-up, but when 5 of the remaining symptomatic patients with normal DAT-binding underwent a second round of DAT-SPECT imaging after 1.5 years, all of these scans were found to be abnormal [61]. Another recent DAT-SPECT study of DLB failed to find a significant correlation between presence of RBD and striatal DAT-binding in DLB patients (with average DLB disease duration

Table 30.3 Dopaminergic imaging in iRBD

	Study sample *n* (*n*♂; average age in years ± SD; average disease duration in months)		Tracer/imaging	Main takeaway	Additional
Presynaptic dopaminergic imaging					
Arnaldi et al. [54]	iRBD 12 PD-iRBD− 16 PD-iRBD+ 24	(12♂; 66.4 ± 7.5; 52) (8♂; 67.2 ± 7.2; N/A) (16♂; 69.4 ± 6.0; 44)	[^{123}I] FP-CIT-SPECT	*[^{123}I]FP-CIT specific binding ratio (SBR)*: • Caudate: PD-iRBD− > iRBD > PD-iRBD+ • Putamen: iRBD > PD-iRBD− > PD-iRBD+	Motor impairment was more severe in PD-iRBD+ patients than PD-iRBD−
Doppler et al. [57]	HC 20 iRBD 18 PD 25	(8♂; 59; N/A) (15♂; 63; 55) (14♂; 63; N/A)	[^{123}I] FP-CIT-SPECT	*Phosphorylated α-synuclein deposits detected in dermal nerve fibers*: HC < iRBD < PD • HC: 0/20 subjects (0%) • iRBD with normal [^{123}I]FP-CIT uptake: 3/8 (37.5%) • iRBD with abnormal [^{123}I]FP-CIT uptake: 7/10 (70%) • PD: 20/25 subjects (80%)	Olfactory function also correlated negatively to increased phosphorylated α-synuclein deposits
Eisensehr et al. [50]	HC 7 iRBD 5 PD 14 (H&YI)	(5♂; 63.0 ± 6.4; N/A) (4♂; 68.5 ± 7.5; "several years") (10♂; 50.3 ± 9.9; 20)	[^{123}I]IPT-SPECT	*Striatal [^{123}I]IPT-binding*: HC > iRBD ≈ PD (ipsilateral to affected side) > PD (contralateral to affected side)	*(See* Table 30.2*, section on Postsynaptic dopaminergic imaging, for more on this article)*

(continued)

Table 30.3 (continued)

	Study sample *n* (*n*♂; average age in years ± SD; average disease duration in months)		Tracer/imaging	Main takeaway	Additional
Iranzo et al. [36]	HC 18 iRBD 43	(12♂; 70.1 ± 7; N/A) (37♂; 70.2 ± 6.9; 114)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: • iRBD: 17/43 (40%) abnormal at baseline *Phenoconversion*: • 8/43 (19%) iRBD converted; of these, 6/8 (75%) had abnormal [^{123}I]FP-CIT uptake at baseline	In combination with transcranial sonography (TCS), [^{123}I]FP-CIT-SPECT could predict iRBD conversion after 2.5 years with 100% sensitivity and 55% specificity
Iranzo et al. [47]	HC 20 iRBD 20	(15♂; 69.5 ± 6.8; N/A) (18♂; 70.6 ± 6; 115)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: HC > iRBD in putamen + caudate bilaterally • iRBD: 10/20 abnormal at baseline (50%) • iRBD: 13/20 abnormal after 3 years (65%), with 3 phenoconverters *Rate of reduction in striatal [^{123}I] FP-CIT-binding*: HC < iRBD < iRBD phenoconverters	N/A
Iranzo et al. [59]	HC 20 iRBD 87	(15♂; 71.0 ± 7.8; N/A) (67♂; 70.0 ± 6.7; 36)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: • iRBD: 51/87 abnormal at baseline (59%) *Phenoconversion*: • 5/36 (14%) iRBD patients with normal uptake converted after 3 years • 20/51 (20%) iRBD patients with abnormal uptake converted after 3 years • Of the 59 iRBD patients who followed up after 5 years, 5/25 (20%) with normal baseline uptake converted vs. 15/34 (44%) with abnormal uptake at baseline	>25% reduction in putaminal [^{123}I] FP-CIT uptake discriminated between iRBD patients with baseline abnormal [^{123}I]FP-CIT-binding who phenoconverted after 3 years vs. those who remained disease free

Kim et al. [52]	HC 12 iRBD 14 PD 14	(8♂; 63.3 ± 5.7; N/A) (11♂; 66.6 ± 4.5; 49) (11♂; 67.0 ± 4.1; N/A)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: • Caudate: HC ≈ iRBD > PD • Putamen: HC > iRBD > PD	No correlation found between polysomnographic tonic or phasic EMG findings and [^{123}I]FP-CIT uptake
Meles et al. [56]	HC 19 iRBD 21 PD 20 DLB 22	(9♂; 62.4 ± 7.5 N/A) (18♂; 61.9 ± 5.4; 83) (16♂; 67.5 ± 8.6; 24) (17♂; 73.7 ± 7; 36)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: • iRBD: abnormal uptake in 9/21 (43%) *([^{18}F]FDG-PET-based) PDRP z-scores*: HC < iRBD < PD < DLB • iRBD patients with abnormal [^{123}I] FP-CIT uptake tended to have higher PDRP scores, but not statistically significant • 7/9 (78%) iRBD patients with abnormal [^{123}I]FP-CIT uptake had suprathreshold PDRP scores • 5/12 (42%) iRBD patients with normal [^{123}I]FP-CIT uptake had suprathreshold PDRP scores	Although trends were seen, there was no direct, significant correlation between PDRP *z*-scores, [^{123}I] FP-CIT-binding, and olfaction *(For more on this article, see* Table 30.3*, Multivariate FDG-PET and blood flow SPECT studies (SSM/PCA)*
Rupprecht et al. [55]	iRBD 28	(20♂; 66.3 ± 8; 81)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: • Of 11 iRBD patients who agreed to [^{123}I]FP-CIT-SPECT, 4/11 (36%) iRBD patients had reduced uptake, 3/4 (75%) particularly in the putamen • Reduced [^{123}I]FP-CIT uptake was correlated with higher UPDRS-III score and younger age of iRBD onset	SN hyperechogenicity on TCS and olfactory dysfunction were not significantly correlated with [^{123}I] FP-CIT uptake

(continued)

Table 30.3 (continued)

	Study sample *n* (*n*♂; average age in years ± SD; average disease duration in months)		Tracer/imaging	Main takeaway	Additional
Stiasny-Kolster et al. [51]	HC 30 RBD 19 (iRBD 6) *(sRBD patients not mentioned here)*	(18♂; 48.2 ± 13.9; N/A) (12♂; 48.4 ± 14.6; 91)	[^{123}I] FP-CIT-SPECT	*Striatal [^{123}I]FP-CIT-binding*: • Of 9 clinical RBD (3 iRBD) patients who agreed to [^{123}I]FP-CIT-SPECT, 2/9 (22%) RBD (2/3 (67%) iRBD) patients had reduced [^{123}I]FP-CIT uptake, particularly in the putamen	Both iRBD patients with reduced [^{123}I] FP-CIT had severe olfactory dysfunction (anosmia)
Stokholm et al. [58]	HC 19 iRBD 20	(19♂; 65.2 ± 4.0; N/A) (17♂; 66.6 ± 6.3; 46)	[^{18}F] FDOPA-PET	*Striatal [^{18}F]FDOPA-binding*: HC > iRBD bilateral putamen • 18/20 (90%) iRBD patients had abnormally reduced striatal [^{18}F]FDOPA uptake • Of these, 7/18 (39%) had reduced uptake in the caudate, all of whom had reduced putaminal uptake as well (6/7 (86%) ipsilateral putamen, 1/7 (14%) bilateral)	Increased [^{11}C]PK11195 uptake in the left SN was correlated with reduced [^{18}F]FDOPA uptake in the ipsilateral caudate *(See* Table 30.4 *for more on this article)*
Postsynaptic dopaminergic imaging					
Eisensehr et al. [50]	HC 7 iRBD 5 PD 14 (H&Y I)	(5♂; 63.0±6.4; N/A) (4♂; 68.5±7.5; "several years") (10♂; 50.3±9.9; 20±11)	[^{123}I] IBZM-SPECT	*Striatal [^{123}I]IBZM-binding*: • iRBD patients had reduced postsynaptic D2 receptors, but it is not statistically significant compared to HC	*(See* Table 30.2*, section on Presynaptic dopaminergic imaging, for more on this article)*

Note: *HC* healthy controls, *N/A* not available/not applicable, *PD* Parkinson's disease, *(i)RBD* (idiopathic) rapid eye movement sleep behavior disorder, *sRBD* subclinical RBD, *PDRP* PD-related (SSM/PCA-computed) metabolic brain pattern, *SN* substantia nigra, *UPDRS-III* unified Parkinson's disease rating scale, *H&Y I/II* Hoehn & Yahr I/II, ♂ male, *SD* standard deviation

1–3 years) [62]. It may therefore be conceivable that patients with iRBD who later develop DLB may not specifically have abnormal DAT-SPECT scans prior to phenoconversion.

30.3.2 Postsynaptic Dopaminergic Imaging

Differences between PD, MSA, and PSP striatal pathology can be evaluated by examining changes in postsynaptic dopamine D2 receptor integrity. Receptor-binding ligands such as [^{11}C]raclopride in PET and [^{123}I]iodobenzamine (IBZM) in SPECT imaging are both used for this purpose (see Fig. 30.1) [63, 64]. Studies have shown that early, untreated PD patients have seemingly compensatory upregulation of D2 receptors; but as the disease progresses, a significant decrease in striatal D2 receptor-binding becomes apparent [65, 66]. D2 receptor-containing neurons are also particularly affected in MSA and PSP [66–68]. However, as D2 receptor-binding reduction in MSA and PSP appears comparable to that of late-stage PD, [^{11}C] raclopride-PET and IBZM-SPECT imaging are not recommended for routine use in the differential diagnosis of these disorders. However, assessing the ratio between DAT- and D2-binding may be useful in differentiating between PD and atypical parkinsonian disorders [69, 70].

As a result of the ambiguous results given by postsynaptic dopaminergic imaging alone, not much information is available on its application to iRBD patients. The few existing studies on this topic have been limited by small sample sizes of specific subgroups of patients and have failed to show significant differences in the imaging between healthy controls, RBD patients, and PD patients [50] (see Table 30.3).

Therefore, it is not currently recommended to use postsynaptic dopaminergic imaging to monitor iRBD progression and predict risk of phenoconversion, although theoretically early D2 receptor decline in MSA may be helpful in identifying iRBD patients who are more likely to phenoconvert to MSA rather than to PD [53].

30.4 Imaging of Non-Dopaminergic Systems

It is known that patients with PD and other parkinsonian disorders are characterized not only by dopaminergic loss in the brain, but also by degeneration of other neurotransmitter systems—including serotonergic, cholinergic, and noradrenergic systems. Using radiotracer imaging, it is possible to see some of these changes in PD patients; however, there is a need for further research of non-dopaminergic imaging in prodromal, premotor PD/DLB patients, and particularly in iRBD.

30.4.1 Serotonergic Imaging

Some radiotracers used for serotonergic imaging in parkinsonian patients are the same ones used in presynaptic dopaminergic imaging, such as [^{123}I]FP-CIT and

[^{123}I]β-CIT. These tracers, in addition to having high DAT-binding affinity, also have some affinity for the serotonin transporter protein (SERT) in the thalamus and midbrain (with a DAT:SERT affinity ratio of 2.8:1 for [^{123}I]FP-CIT and 1.7:1 for [^{123}I]β-CIT) [71]. Because DAT and SERT expression are almost entirely segregated to different parts of the brainstem, it is possible to use [^{123}I]FP-CIT- and [^{123}I]β-CIT-SPECT to adequately visualize brain serotonergic activity [71–73]. Additionally, [^{18}F]FDOPA uptake has also been correlated to serotonergic activity in the raphe nuclei of PD patients [74].

Not only are SERT levels decreased in PD patients compared to healthy controls, but several studies have established that it is possible to use [^{123}I]β-CIT and [^{123}I]FP-CIT SERT imaging to successfully distinguish among various types of parkinsonian disorders [71–73]. However, so far these findings have evaded applicability to the early or prodromal stages of disease: one study comparing SERT-binding in early-stage PD and MSA could not find a significant difference between the two patient groups, while another study aimed specifically at iRBD patients did not find reduced SERT-binding compared to healthy controls [75, 76].

However, there are other tracers available for evaluating serotonergic function which are known to have a higher specificity for SERT: among them, [^{11}C]3-amino-4-(2-dimethyl-aminomethylphenylsulfaryl)-benzonitrile ([^{11}C]DASB) [77]. It is known that [^{11}C]DASB-binding is decreased in advanced PD patients [78]. One study of early PD patients found that while [^{11}C]DASB uptake was diffusely reduced compared to healthy controls, there was relative sparing of serotonergic function in the caudal brainstem [79]. Another study found that [^{11}C]DASB uptake was not significantly reduced in early PD patients compared to healthy controls; however, it was negatively correlated to striatal DAT uptake [80]. It is possible that this may reflect early compensatory serotonergic changes preceding onset of PD motor symptoms. To date, the only study investigating [^{11}C]DASB uptake in RBD patients examined differences between PD-RBD+ and PD-RBD− patients, rather than in premotor iRBD patients, and did not find significant differences in [^{11}C]DASB uptake between the two groups [81].

30.4.2 Cholinergic Imaging

It is established that damage to cholinergic neurons projecting from the nucleus basalis of Meynert (NBM) in the basal forebrain or pedunculopontine nucleus (PPN) in the brainstem plays a key role in the pathogenesis of PD-associated dementia. This notion is supported by evidence of greater cognitive dysfunction in PD patients who take anticholinergic medications [82]. Several tracers have been used to examine the integrity of the cholinergic system in parkinsonian patients, including presynaptic cholinergic markers such as [^{11}C]methylpiperidyl propionate acetylcholinesterase ([^{11}C]PMP) and N[^{11}C]methyl-4-piperidyl acetate ([^{11}C]MP4a), which are direct markers of AChE activity; [^{123}I]iodobenzovesamicol (IBVM), an analogue of vesamicol and *in vivo* marker of vesicular ACh transporter-binding; and postsynaptic cholinergic markers such as 5[^{123}I]iodo-3[2(S)-2-azetidinylmethoxy]

pyridine ([^{123}I]5IA) and 2[^{18}F]F-A-85380 ([^{18}F]2FA), which are specific for brain nicotinic acetylcholine receptors (α4β2 nAChR) [83].

One [^{11}C]PMP-PET imaging study examining differences between PD-RBD+ and PD-RBD− patients found that PD-RBD+ patients exhibited significantly decreased AChE activity in neocortical, thalamic, and limbic cortical regions compared with PD-RBD− patients [81]. Based on these results, it is possible that cholinergic denervation may play a particularly defining role in the pathophysiology of PD among RBD patients, although [^{11}C]PMP uptake in iRBD patients still needs to be further investigated. However, other studies have shown mixed results on [^{11}C]PMP-PET imaging among PD patients—one limitation which must be considered is that [^{11}C]PMP does not accurately reflect AChE activity in areas with very high cholinergic activity, such as in the striatum [84].

Studies of [^{11}C]MP4a-PET imaging have found [^{11}C]MP4a-binding to be a useful disease progression marker and tool for differentiating among various parkinsonian disorders. Multiple studies have shown decreased [^{11}C]MP4a uptake in PD patients when compared to controls, with particularly decreased uptake in DLB as well as demented PD patients [85–87]. Another study found that uptake differed significantly between PD and PSP patients, with cortical cholinergic loss more pronounced in PD patients, and thalamic cholinergic loss more marked in PSP patients [88].

An IBVM-SPECT imaging study done in DLB patients found significantly decreased IBVM-binding to vesicular ACh transporter compared to healthy controls [89]. Another IBVM-SPECT study on MSA-RBD+ patients showed decreased IBVM-binding in the thalamus compared to controls, but IBVM uptake did not correlate to the severity of REM atonic loss [90].

A [^{123}I]5IA-SPECT imaging study of cognitively-intact early PD patients (<7 years since diagnosis) found that disease duration was positively correlated to increased postsynaptic nAChR density in the putamen ipsilateral to the most-affected body side. As most anatomopathological studies show loss of nAChR agonist-binding in the striatum of advanced PD patients, this study's findings may point to an early cholinergic compensatory mechanism in the development of PD [84].

30.4.3 Noradrenergic Imaging

As PD progresses, degeneration is classically seen in the noradrenergic neurons projecting from the Locus Coeruleus (LC) in the brainstem [91]. A number of cardiac noradrenergic imaging studies have been done in early DLB and RBD patients with metaiodobenzylguanidine ([^{123}I]MIBG), a radiolabeled analogue of norepinephrine used in [^{123}I]MIBG-SPECT scans [92–94] (see Chap. 33 for more details). However, there is currently a shortage of studies examining noradrenergic imaging in the brain, in particular with regard to prodromal PD/DLB presenting clinically as iRBD. Part of the problem is that a highly specific radiotracer for the norepinephrine transporter protein (NET) in the LC is not yet commercially available [95]; [^{123}I]MIBG is unfortunately not well-visualized intracranially [96].

Nonetheless, just as in dopaminergic and serotonergic imaging, it is possible to employ [^{123}I]FP-CIT-SPECT and [^{18}F]FDOPA-PET to observe noradrenergic function in the brain. Although the affinity of [^{123}I]FP-CIT is much lower to NET than for DAT or SERT, when examining an area such as the LC where NET expression predominates, it is possible to use it as a marker of noradrenergic integrity. One study therefore found significantly increased LC [^{123}I]FP-CIT-binding in early PD patients compared with healthy controls [97]. Another [^{18}F]FDOPA-PET study found that while LC [^{18}F]FDOPA uptake was initially increased in early PD patients, after approximately 3 years of follow-up it had decreased to subnormal levels [98]. These studies are consistent with the idea that noradrenaline reuptake is increased in the early stages of disease in compensation for dopaminergic degeneration.

Another radiotracer specific for DAT and NET which has been used to image the noradrenergic system in PD patients is [^{11}C]RTI-32. One [^{11}C]RTI-32-PET study has found that depression in PD patients correlated with lower LC [^{11}C]RTI-32 uptake [99]. However, as of now this tracer has not yet been employed in noradrenergic studies of early PD or iRBD patients.

Lastly, a recent PET study examined [^{11}C]MeNER uptake in 16 PD-RBD+ versus 14 PD-RBD− patients and 12 control subjects. [^{11}C]MeNER is a NET-specific reboxetine analogue. PD-RBD+ patients were found to have widespread reduced [^{11}C]MeNER-binding which correlated to amount of REM sleep without atonia, cognitive impairment, EEG slowing, and orthostatic hypotension as compared to the PD-RBD− patients and especially healthy controls. Low thalamic [^{11}C]MeNER distribution volume ratios also correlated to low LC-to-pons ratios on neuromelanin MRI [100]. This supports the idea that noradrenergic degeneration may contribute to non-motor symptomatology, and that PD patients with RBD tend to have a more severe disease trajectory than those without. However, [^{11}C]MeNER-PET has not yet been evaluated as a tracer in prodromal or early parkinsonian cases.

30.5 Functional Imaging Studies

The aforementioned studies focus on structural brain changes caused by neurodegeneration (i.e., loss of grey *and* white matter; destruction of dopaminergic neurons). However, in PD and in neurodegenerative diseases in general, it is known that functional changes often precede structural changes. Before causing neuronal death, accumulation of abnormal α-synuclein in neurons is thought to interfere with synaptic signaling, thereby inducing changes in neuronal activity. Neuronal activity can be measured indirectly by mapping aspects of neurovascular coupling, such as metabolic activity (FDG-PET), cerebral blood flow (perfusion SPECT), and blood oxygenation (functional MRI). Classically, signal changes in discrete regions are compared between controls and patients to identify areas of abnormal neuronal activity.

However, brain regions do not operate in isolation, but are part of intricate brain networks. In other words, neuronal activity in one region is influenced by interactions between connected areas distributed throughout the entire brain. It is also thought that neurodegeneration occurs within structurally and functionally

connected networks [101]. It is therefore of interest to study the network-level changes induced by neurodegenerative processes. In functional neuroimaging studies, this is achieved by functional connectivity analyses. Such analyses aim to find the predominant pattern(s) of correlations (with principal or independent component analysis) or test whether a particular correlation between signals from two remote brain regions is significant [102]. Functional connectivity patterns can be applied as a phenotype to predict the manifestation of a disease in individual subjects. This is highly relevant in the context of iRBD. To prevent performance confounds, functional connectivity in RBD and α-synucleinopathies is typically assessed in the resting state, and not in task conditions.

30.5.1 Resting-State Functional MRI

Brain activity at rest can be investigated by using resting-state functional MRI (rs-fMRI) to assess temporal fluctuations in the blood-oxygen-level dependent (BOLD) signal [103]. One study employing rs-fMRI in iRBD reported reduced functional connectivity between the left putamen and the SN. Functional connectivity between these regions was nonetheless higher in iRBD than PD, indicating a continuous spectrum of decline in functional connectivity [104]. Another study exploring the potential of rs-fMRI to quantify basal ganglia dysfunction in iRBD patients was performed using voxel-wise and region-of-interest analyses of the basal ganglia network, with direct comparisons to controls and PD patients [105]. Results showed widespread aberrant connectivity within the basal ganglia network in iRBD patients, with abnormalities being most prominent within the basal ganglia themselves. Further extrastriatal changes were observed predominantly in the frontal lobes. Connectivity measures of basal ganglia network dysfunction could differentiate both iRBD and PD from controls with high sensitivity (96%) and specificity (74% for iRBD, 78% for PD). A similar study was performed in data from the Parkinson's Progression Markers initiative (PPMI). Region-to-region and seed-to-voxel functional connectivity matrices were determined from rs-fMRI data of 17 prodromal PD patients (13 with iRBD and 4 with hyposmia) and 18 controls. The prodromal group displayed reduced striato-thalamo-pallidal functional connectivity. This feature could differentiate between the two groups (sensitivity of 93.3% and specificity of 82.3%). Functional connectivity changes were limited to the basal ganglia and did not include other subcortical or cortical regions [106]. These studies indicate a potential for connectivity measures of basal ganglia network dysfunction as an indicator of early basal ganglia dysfunction.

Functional neuroimaging may help to further characterize PD subtypes, as it has been shown that there is an rs-fMRI-measured correlation between PD-RBD+ and postural dysfunction, with impaired functional connectivity seen in a locomotor network between the PPN and supplementary motor area [107]. It was also found that daytime somnolence may be linked to RBD via alterations in the functional connectivity of an arousal network between the PPN and anterior cingulate cortex. However, these results were obtained in PD-RBD+ patients post-phenoconversion.

30.5.2 Glucose Metabolism and Cerebral Blood Flow

Both glucose metabolism and cerebral blood flow are related to synaptic activity [108]. The radiotracer [^{18}F]Fluorodeoxyglucose (FDG) is analogous to glucose, and FDG-PET provides an index for the first step of the cellular glycolytic pathway. Several tracers are available to measure cerebral blood flow, but studies in RBD are limited to ^{99m}Tc-Ethylene Cysteinate Dimer (ECD)-SPECT. It must be noted that most FDG-PET and perfusion SPECT studies evaluate *relative* signal increases and decreases. For absolute quantification of metabolism or blood flow, arterial blood sampling is required, which is invasive and time-consuming, and therefore rarely performed.

Although glucose metabolism and cerebral blood flow are closely coupled [109, 110], dissociations can occur, especially in response to medication (e.g., levodopa [111]). However, in neurodegenerative diseases, similar disease patterns have been obtained with FDG-PET and ECD-SPECT. Compared to controls, PD patients typically show relatively increased metabolism or blood flow in the cerebellum, brainstem, putamen/pallidum, thalamus, and sensorimotor cortex, and relatively decreased activity in the lateral frontal and parietooccipital areas [112]. Relative hypermetabolism in subcortical areas is thought to reflect dysfunction in basal ganglia networks, as FDG uptake in these areas has been shown to correlate with firing rates of the subthalamic nucleus and to the severity of motor symptoms [113]. Cortical hypometabolism precedes atrophy [114], progresses with disease duration, and is related to cognitive decline [115]. The metabolic disease pattern of DLB is similar to that of PD, but is characterized by more severe occipital hypofunction [116–118]. In contrast, the MSA pattern is distinct from PD as it is characterized by *hypo-* rather than hyperactivity in the basal ganglia and cerebellum [116, 117]. The described PD, DLB, and MSA patterns have been identified with both univariate (i.e., voxel-by-voxel) and multivariate (i.e., connectivity) analyses [112].

30.5.3 Univariate Perfusion SPECT Studies

Similar to PD, patients with iRBD show increased perfusion in the pons, putamen, and hippocampus compared to healthy controls [3, 119]. Decreased perfusion has been reported in varying cortical areas including the temporal [3, 119–121], parietal [3, 119–122], occipital [119, 121, 122], frontal [3, 119, 123], posterior cingulate cortex [120], limbic, and cerebellar regions [122]. Inconsistencies reported between groups may be related to heterogeneity of RBD populations as well as to methodological differences.

One study found significant hypoperfusion of the frontal cortex and hyperperfusion of the pons, putamen, and left hippocampus in iRBD patients (n = 20) compared to controls (n = 20). In iRBD patients, hypoperfusion of the extrastriate visual cortex was correlated with poorer color discrimination, and hypoperfusion of the anterior parahippocampal gyrus bilaterally was correlated to loss of olfactory discrimination [119].

In a subsequent study, brain perfusion was compared between iRBD patients with mild cognitive impairment (MCI; $n = 10$) and iRBD patients with normal neuropsychological examinations ($n = 10$). As is the case in PD, hypoperfusion of the occipital, parietal, and temporal cortex was more pronounced in iRBD patients with MCI than those without MCI. iRBD patients with MCI also had more pronounced hyperperfusion of the hippocampus, putamen, and left paracentral gyrus when compared to cognitively normal iRBD patients [123].

Finally, Dang-Vu et al. studied the association between regional cerebral blood flow changes in 20 iRBD patients at baseline and subsequent conversion to PD or DLB over the course of 3 years of clinical follow-up. Ultimately, five iRBD patients converted to PD, and five converted to DLB. Hippocampal perfusion was increased in converters compared to non-converters and was significantly correlated with motor and color vision scores [124]. No clear differences in cerebral blood flow were reported between iRBD patients who converted to PD ($n = 5$) and those who converted to DLB ($n = 5$).

Sakurai et al. performed blood flow SPECT in nine iRBD patients at baseline and after approximately 2 years [121]. Three-dimensional stereotactic surface projections (3D-SSP [125]) were created for each scan and compared with data from 18 controls. Overall, patients had lower cerebral blood flow in the bilateral parietotemporal and occipital areas. Although these nine patients did not phenoconvert during the study, there was a progressive decrease in perfusion of the posterior cingulate, supporting the notion of a progressive neurodegenerative disease process.

In summary, these studies suggest a role for relative hippocampal hyperperfusion and progressive cortical hypoperfusion in the prediction of phenoconversion from iRBD to PD or DLB. Involvement of the hippocampus in iRBD appears to be a consistent finding in neuroimaging studies. The significance of hippocampal hyperactivity, however, remains unclear. It has been suggested that hippocampal activation at baseline may be a compensatory response to sustain cognitive performance despite progressive dysfunction in other brain regions [126]. Alternatively, it may result from changes in networks connecting the basal ganglia with the limbic system [127]. Further longitudinal studies should directly address the pathophysiological meaning of hippocampal hyperactivity, and clarify whether it truly reflects a compensatory mechanism. Progressive cortical dysfunction may be more pronounced in subjects who develop PD dementia or DLB, but this is currently not definitively known (see Table 30.4).

30.5.4 Univariate FDG-PET Studies

Few univariate FDG-PET studies of iRBD exist. Caselli et al. were able to quantify absolute cerebral glucose metabolism (i.e., with dynamic FDG-PET scanning and arterial blood sampling) in 17 patients with "dream-enacting behavior" (polysomnography was not performed) and 17 controls [120]. These probable RBD patients had lower metabolism in the right medial parietal cortex and posterior cingulate compared to controls. Areas of increased metabolism were not identified.

Table 30.4 Metabolism and blood flow in iRBD

	Study sample *n* (*n*♂; age in years ± SD; iRBD disease duration in years ± SD)		Method	Cerebral blood flow/metabolism group comparisons (usually iRBD versus HC)	Additional results
Cerebral blood flow SPECT studies (univariate)					
Mazza et al. [3]	iRBD 8 HC 9	(7♂; 69.9 ± 8.2; 7.5 ± 4.8) (67.4 ± 6.8)	[^{99m}Tc]ECD + whole-brain analysis using SPM2 *t*-test, $P < 0.01$ (50 contiguous voxels), no correction for multiple comparisons	↑ *Pons, putamen, R hippocampus* ↓ *Frontal, temporal, and parietal cortex*	
Hanyu et al. [122]¶	iRBD 24 HC 18	(21♂; 68 ± 7; 6 ± 5) (9♂; 70 ± 8)	[^{99m}Tc]ECD + whole-brain analysis using SPM2 *t*-test, $P < 0.01$ (50 contiguous voxels), no correction for multiple comparisons	↑ *None* ↓ *Parietal (precuneus), occipital, limbic (uncus), R cerebellar vermis*	No significant correlation was found among rCBF changes and PSG variables or iRBD duration
Vendette et al. [119]†	iRBD 20 HC 20	(13♂; 65.0 ± 7.7; 11.1 ± 8.7) (15♂; 67.4 ± 6.4)	[^{99m}Tc]ECD + whole-brain analysis using SPM2 *t*-test, $P < 0.01$ (50 contiguous voxels), no correction for multiple comparisons	↑ *Pons, putamen, hippocampus, temporal, postcentral gyrus* ↓ *Frontal, medial parietal cortex (precuneus)*	Errors on color discrimination correlates (−) with rCBF in frontal, temporal, temporo-occipital regions and (+) with occipital, posterior cingulate, cerebellum Olfaction correlates (+) with rCBF anterior parahippocampal gyrus, occipital, temporal, cerebellum

Vendette et al. [123]†	*iRBD+MCI 10* *iRBD-MCI 10* *HC 20*	(7♂; 68.5 ± 5.7; 13.4 ± 10.0) (5♂; 65.64 ± 8.22; 8.0 ± 5.8) (15♂; 67.4 ± 6.4)	[^{99m}Tc]ECD + region of interest analysis using SPM2 (*t*-test, three between-group comparisons), $P < 0.05$ (peak-voxel level), corrected for multiple comparisons	*iRBD+MCI versus iRBD-MCI* ↑ R hippocampus, putamen, L paracentral gyrus ↓ Occipital, superior temporal *iRBD+MCI versus HC*: ↑ R hippocampus, L paracentral gyrus ↓ Frontal, occipital, precuneus/angular gyrus, L superior temporal *iRBD-MCI versus HC*: ↑ R hippocampus ↓ Frontal cortex	
Dang-vu et al. [124]† (follow-up)	iRBD (−) 10 iRBD (+) 10 HC 10	(8♂; 65.5 ± 7.2; 17.7 ± 11.6) Did not convert (8♂; 70.3 ± 6.6; 10.5 ± 5.8) Converted: 5 PD, 5 DLB N/A	[^{99m}Tc]ECD, SPM8, two-sample *t*-test; correlation between rCBF and clinical scores (UPDRS-III, color vision, olfaction). $P < 0.05$, correction for multiple comparisons Subjects were scanned at baseline; clinical follow-up was 3 years on average	*iRBD(+) versus iRBD(−)* ↑ Hippocampus, putamen ↓ None *iRBD(+) versus HC* ↑ Hippocampus, pons ↓ None *iRBD(−) versus HC* ↑ None ↓ None	*Correlations* + UPDRS-III and R hippocampus + Olfaction and medial frontal gyrus + Color vision and pons, L hippocampus
Sakurai et al. [121]¶ (follow-up)	iRBD 9 HC 18	(7♂; 71.1 ± 3.2; 6.5 ± 5.1) (9♂; 70.4 ± 8.1)	[^{123}I]IMP at baseline and follow-up (interval 22.8 ± 9.2 months). 3D-SSP and *t*-test on *z*-scores (with reference to control mean)	*iRBD follow-up versus iRBD baseline* ↑ None ↓ R posterior cingulate	

(continued)

Table 30.4 (continued)

	Study sample *n* (*n*♂; age in years ± SD; iRBD disease duration in years ± SD)		Method	Cerebral blood flow/metabolism group comparisons (usually iRBD versus HC)	Additional results
[^{18}F]FDG-PET studies (univariate)					
Caselli et al. [120]	iRBD 17* HC 17	(6♂; 59 ± 11; N/A) (59 ± 11) * *dream enactment behavior, no PSG*	[^{18}F]FDG, region of interest	↑ N/A ↓ Parietal, temporal, and posterior + anterior cingulate	
Fujishiro et al. [128]+	iRBD 9* HC	(7♂; 71.0 ± 5.6; 4.5 ± 4.0) Normative database, NA * *dream enactment behavior, no PSG*	[^{18}F]FDG, 3D-SSP images compared to normative database All patients showed reduced cardiac [^{123}I]-MIBG levels	↓ Primary visual cortex (n = 4) ↓ L anterior cingulate, R frontal, R anterior temporal (n = 5)	
Fujushiro et al. [129]+ (follow-up)	iRBD 7* HC 77	(4♂; 71.6 ± 4.2; 3.9 ± 3.2) Normative database, NA * *dream enactment behavior, no PSG*	[^{18}F]FDG, 3D-SSP images compared to normative database 6/7 patients showed reduced cardiac [^{123}I]-MIBG levels	Follow-up: 47 ± 5 months Non-converters (n = 3): ↓ Primary visual cortex Converters to DLB (n = 4): ↓ Primary visual cortex, lateral occipital cortex, parietal cortex	

Ge et al. [130]‡	iRBD 21 HC 21	(17♂; 65.0 ± 5.6; 5.7 ± 3.5) (17♂; 62.5 ± 7.5)	[^{18}F]FDG, SPM two-sample *t*-test (voxel-by-voxel)	↑ Hippocampus, cingulate, SMA, pons ↓ Occipital cortex	*Correlations*: iRBD duration with CMRglc cerebellar vermis (+) and medial frontal gyrus (−) Chin EMG activity with CMRglc hippocampus (+) and posterior cingulate (−)
Multivariate FDG-PET and blood flow SPECT studies (SSM/PCA)					
Holtbernd et al. [146] (follow-up)	**Cohort A** iRBD 10 HC 10 **Follow-up:** **Cohort B** iRBD 17 iRBD→ MSA *n* = 3 HC 17	[^{18}F]FDG-PET *(10♂;* *63.5 ± 9.4;* N/A) *(N/A; 62.7 ± 8.6)* ECD-SPECT (N/A; 68.9 ± 4.8;N/A) Follow-up: 4.6 ± 2.5 years (N/A; 59 ± 8.2; N/A) Follow-up: 3.2 ± 1.0 years (N/A; 66.6 ± 6.0)	[^{18}F]FDG-PET/ECD-SPECT Tracer uptake in volumes of interest (pons, cerebellum, putamen/globus pallidus, thalamus, sensorimotor, lateral premotor, parietal association cortex) were compared between iRBD and controls in both cohorts with a Student's *t*-test. These volumes of interest reflect the main nodes of the PDRP PDRP expression was calculated (at baseline) in both cohorts. In cohort B, five iRBD patients converted to PD and three to DLB	↑ Pons, putamen/pallidum, thalamus ↓ None Converters versus non-converters: ↑ Pons	PDRP expression was significantly higher in iRBD compared to HC in both cohorts ($P < 0.04$) PDRP expression was higher in iRBD patients who converted ($n = 8$) compared to those who did not ($n = 9$), $P < 0.03$ Patients who later developed MSA did not express the PDRP

(continued)

Table 30.4 (continued)

	Study sample *n* (*n*♂; age in years ± SD; iRBD disease duration in years ± SD)		Method	Cerebral blood flow/metabolism group comparisons (usually iRBD versus HC)	Additional results
Wu et al. [147][‡]	**Cohort A** iRBD 21 HC 21 **Cohort B** iRBD 15 HC 15 **Cohort C** PD H&Y I PD H&Y II-III	(17♂; 65.0 ± 5.6; 5.7 ± 3.5) (17♂; 62.5 ± 7.5) (12♂; 65.5 ± 6.0; 5.5 ± 4.0) (10♂; 60.5 ± 7.6) (12♂; 62.6 ± 5.0) (5♂; 56.9 ± 12.2)	[^{18}F]FDG-PET The iRBD-RP was identified in cohort A with SSM/PCA, and expression of the iRBD-RP was calculated in cohort B + C and compared between groups Expression of the PDRP was calculated in each cohort and compared between groups	iRBD-RP: ↑ Pons, thalamus, medial frontal + sensorimotor areas, hippocampus, supramarginal + inferior temporal gyri, and posterior cerebellum ↓ Occipital and superior temporal regions	iRBD expression was higher in iRBD patients and mild PD patients compared to controls but decreased with disease progression iRBD patients expressed the PDRP. PDRP expression was higher in PD patients compared to iRBD
Meles et al. [56][§]	HC 19 iRBD 21 PD 20 DLB 22	(9♂; 62.4 ± 7.5) (18♂; 61.9 ± 5.4; 6 years) (16♂; 67.5 ± 8.6) (17♂; 73.7 ± 7)	[^{18}F]FDG-PET/[^{123}I]FP-CIT-SPECT PDRP expression was calculated in each cohort and compared between groups Correlations between PDRP expression, [^{123}I]FP-CIT-binding, and olfaction scores (Sniffin' Sticks) were tested for significance	PDRP expression: HC < iRBD < PD < DLB • iRBD patients with abnormal [^{123}I]FP-CIT uptake tended to have higher PDRP scores, but not statistically significant • 7/9 (78%) iRBD patients with abnormal [^{123}I]FP-CIT uptake had suprathreshold PDRP scores • 5/12 (42%) iRBD patients with normal [^{123}I]FP-CIT uptake had suprathreshold PDRP scores	Although trends were seen, there was no direct, significant correlation between PDRP z-scores, [^{123}I]FP-CIT-binding, and olfaction *(See* Table 30.2*, Presynaptic dopaminergic imaging, for more on this article)*

Meles et al. [152]§	**Cohort A** iRBD 21 HC 19 **Cohort B** iRBD 9 HC 13 **Cohort C** PD 38 HC 44	(18♂; 61.9 ± 5.4; 6 years) (9♂; 62.4 ± 7.5) (8♂; 64.2 ± 6.3, 4 years) (9♂; 61.3 ± 8.6) (25♂; 71.6 ± 6.9) (32♂; 68.8 ± 8.7)	[^{18}F]FDG-PET The iRBD-RP was identified in cohort A with SSM/PCA, and expression of the iRBD-RP was calculated in cohorts B+C and compared between groups Expression of the PDRP was calculated in each cohort and compared between groups	iRBD-RP: ↑ Cerebellum, brainstem, thalamus, sensorimotor cortex, and hippocampus ↓ Middle cingulate, temporal, occipital, and parietal cortex	Both the PDRP and the iRBD-RP increased across groups (HC<iRBD<PD) PDRP/iRBDRP *z*-scores: PDHY1 = PDHY2-3 PD-RBD+ = PD-RBD− PDNC < PDMCI

Studies with overlapping datasets are indicated by (¶ † ‡ + §)

Fujishiro et al. studied nine patients with a history of recurrent dream-enacting behavior (none of whom underwent polysomnography) [128]. Patients did not have dementia or parkinsonism, but all patients did have abnormal [^{123}I]MIBG cardiac scans, suggesting the presence of Lewy body disease. The FDG-PET scans of these nine patients were compared to a normal database using 3D-SSP. Most patients (8/9) had parietal hypometabolism. In addition, four patients showed occipital hypometabolism, and five patients had hypometabolism of the anterior cingulate, frontal lobe, and temporal lobe. A consecutive follow-up study (39–54 months later) of seven patients showed that iRBD patients who later developed parkinsonian signs without dementia had hypometabolism of the primary visual cortex, whereas iRBD patients who later developed DLB had hypometabolism of the parietal and lateral occipital cortex in addition to the primary visual cortex [129].

A larger cross-sectional FDG-PET study of 21 polysomnographically-confirmed RBD patients revealed increased metabolism in the hippocampus, cingulate, supplementary motor area, and pons, and decreased metabolism in the occipital cortex as compared to 21 controls [130]. RBD duration was positively correlated with cerebellar metabolism, and negatively with FDG uptake in the medial frontal cortex. The severity of REM sleep atonia loss was related to hippocampal hypermetabolism and posterior cingulate hypometabolism.

30.5.5 Network Studies of Metabolism and Blood Flow

In the studies described in the previous section, regional differences in mean glucose metabolism or blood flow were typically compared between patients and controls with univariate models (i.e., in SPM). However, functional connectivity-type analyses have also been applied to perfusion SPECT and metabolic PET data in neurodegenerative diseases. A well-validated and promising approach is the scaled subprofile model and principal component analysis (SSM/PCA) method. Using SSM/PCA, disease-related patterns have been identified in several neurodegenerative disorders [116, 131–133]. An important advantage of this approach is that once a pattern is identified, the degree of its expression can be quantified in any [^{18}F] FDG-PET scan. The degree of pattern expression is reflected by the subject score. This constitutes a single numerical value that can be useful in the differential diagnosis, but can also be used to investigate the relationship between brain metabolism and certain clinical scales.

The PD-related pattern (PDRP) could be identified with SSM/PCA in data from both FDG-PET and perfusion SPECT, although the FDG-PET-derived pattern performed better in classifying new subjects [125]. The PDRP is characterized by relatively increased activity in the cerebellum, pons, putamen/pallidum, thalamus, and sensorimotor cortex, and decreased activity in the lateral frontal and parietooccipital areas. This typical topography was identified in several independent cohorts worldwide [132, 134–138] (Fig. 30.2). The MSA-related metabolic brain pattern (MSARP) and Progressive Supranuclear Palsy (PSP)-related pattern (PSPRP) are distinct from the PDRP. Subject scores derived from degree of disease-related pattern expression

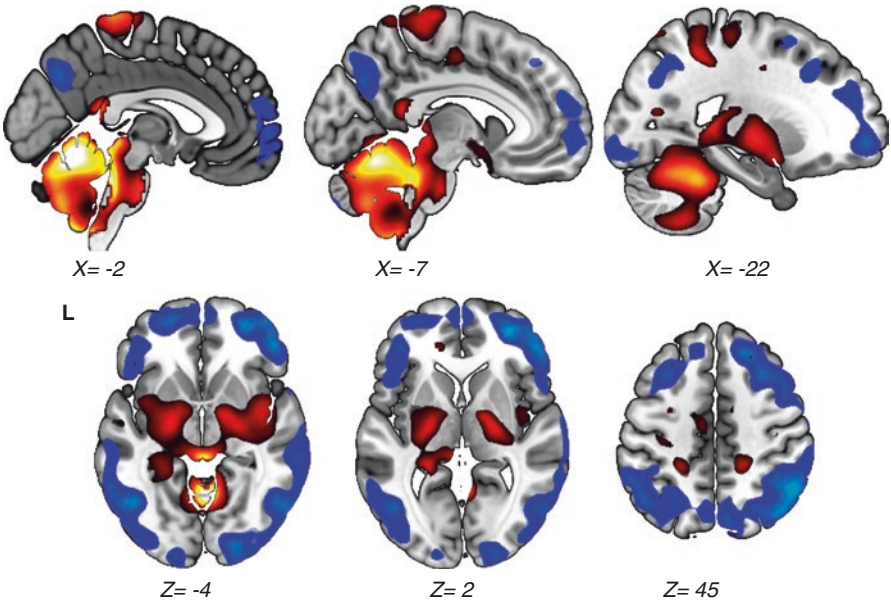

Fig. 30.2 Visual representation of the Parkinson's disease-related pattern (PDRP), identified in a cohort of 17 controls and 19 patients using SSM/PCA (Teune et al. 2014). Stable voxels (90% confidence interval not straddling zero after bootstrap resampling) of the PDRP are visualized by overlaying them on a T1 MRI template. Positive voxel weights are red (to indicate relative hypermetabolism) and negative voxel weights are blue (for relative hypometabolism). *L* left. Coordinates in the axial (*Z*) and sagittal (*X*) planes are in Montreal Neurological Institute (MNI) standard space

can be used to differentiate between conditions with high diagnostic accuracy [139, 140]. SSM/PCA-based image classification was shown to have better sensitivity and replicability compared to univariate approaches [141, 142].

The PDRP is also a marker for disease progression. Continuous increases in PDRP expression are associated with progressive motor impairment and dopaminergic denervation in PD patients [143–145]. Moreover, PDRP expression was found to be elevated in the presymptomatic hemisphere (i.e., ipsilateral to the symptomatic body side) in patients with early-stage PD with unilateral motor involvement [145]. This suggests that PDRP activity may already be present before the onset of key motor symptoms. Three studies have shown that expression of the PDRP was elevated in iRBD patients compared to controls [56, 146–148].

In a cohort of 20 patients, high baseline PDRP expression (a PDRP subject score of >1) on brain perfusion imaging (^{99m}Tc-ECD-SPECT) was more likely in iRBD patients (n = 8) who developed PD or DLB 4.6 ± 2.5 years after getting scanned [146].

The relationship between PDRP expression, putaminal DAT-binding, and olfaction in iRBD patients (n = 21) was also explored [56]. Although a trend was observed, PDRP subject scores and DAT-binding were not significantly correlated (r = −0.39, P = 0.09). In PD studies, only a modest correlation has been found

between DAT-binding and PDRP subject scores, which may point to a partly non-dopaminergic genesis of the PDRP [146].

We also described a subgroup of patients who had PDRP scores in the range of PD patients, but with normal DAT-binding [56]. We speculate that abnormal metabolism, reflected by a high PDRP score, may precede significant loss of DAT-binding. It is also conceivable that these patients will develop DLB, as it has been shown that DLB patients may initially have unremarkable DAT-SPECT scans [61].

Interestingly, we also identified one patient with an abnormal DAT-SPECT who expressed the MSARP, but not the PDRP (unpublished data; Fig. 30.3). We speculate that this individual may develop MSA on long-term follow-up. This would be in line with results from Holtbernd et al., who describe low PDRP scores in three RBD patients who ultimately developed MSA 4.3, 2.5, and 2.7 years after being scanned [146]. Expression of the MSARP was not reported in that study.

In our Dutch-German cohort [56], patients' level of olfaction was also tested using Sniffin' Sticks and divided into two groups; those with total olfaction scores (TDIs) <18, and those with TDIs ≥18. This is in line with a previous study by Mahlknecht et al. which showed that a baseline TDI score of <18 was associated with an elevated risk of conversion to PD or DLB within 5 years of follow-up [149]. Although PDRP expression was higher in patients with hyposmia (TDI < 18), PDRP and olfaction scores were not significantly correlated.

Longitudinal assessment of our cohort is underway and may give important insights into the relationship between DAT-binding, PDRP expression, olfaction, and phenoconversion. PDRP expression may provide complementary information to other markers such as DAT-binding and olfaction [56]. In contrast to olfaction [150], the PDRP is a progression marker [144]. Moreover, PDRP expression is useful in the differential diagnosis of parkinsonian disorders [116] (Fig. 30.3), whereas DAT-imaging is not [151].

To understand the brain changes which occur in the iRBD stage, the RBD-related pattern (iRBDRP) has also been studied with SSM/PCA. Wu et al. describe an RBDRP which is characterized by relative hypermetabolism of the pons, thalamus, medial frontal and sensorimotor areas, hippocampus, supramarginal and inferior temporal gyri, and posterior cerebellum, and relative hypometabolism in the occipital and superior temporal regions. As expected, the iRBDRP was significantly expressed in a second cohort of iRBD patients, and also in the least-affected hemisphere of PD patients with early, unilateral PD. However, iRBDRP subject scores were lower in patients with more advanced PD, indicating that the metabolic changes from iRBD to advanced PD do not follow one pattern. The authors speculate that the RBDRP topography breaks down with disease progression [147].

Our group recently identified the RBDRP in 21 iRBD patients and 19 controls. Our iRBDRP was characterized by altered metabolism in many of the same regions: increased metabolism in the thalamus, pons, and hippocampus, and decreased in the temporal and occipital cortex. However, hyperactivity in the cerebellum was a prominent feature of our RBDRP, and occipital hypometabolism was less pronounced. Taken together, our iRBDRP was more similar to the PDRP than the one described by Wu et al. Indeed, our iRBDRP was expressed in both early and more

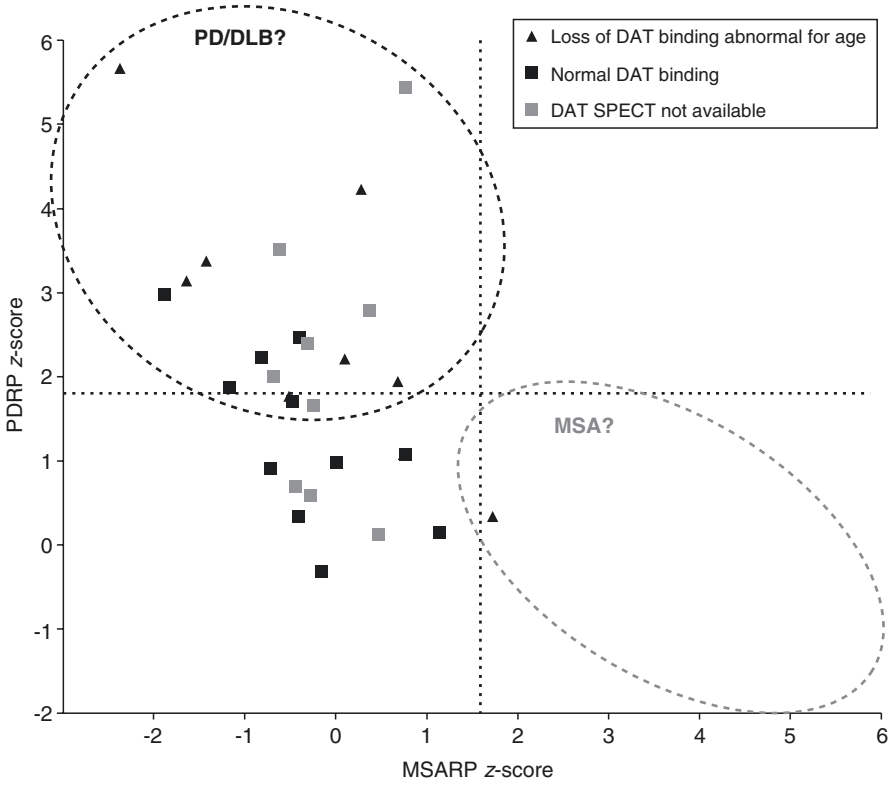

Fig. 30.3 PDRP (*y*-axis; threshold $z = 1.8$) and MSARP (*x*-axis; threshold $z = 1.6$) expression *z*-scores in 30 iRBD patients. Black squares indicate normal DAT-binding for age, while black triangles indicate abnormal DAT-binding for age. Grey squares indicate patients who did not undergo DAT-SPECT

advanced PD patients. We concluded that our iRBDRP is likely a predecessor of the PDRP, and, similarly to the PDRP, its expression *increases* with disease progression. These differences in topographies may be explained both by heterogeneity in patient samples and methodological differences [152] (Table 30.4).

Conclusion

RBD is known to be an initial symptom of progressive neurodegeneration, but it can be challenging to set individual prognoses concerning the risk of subsequent phenoconversion and likelihood of developing a distinct α-synucleinopathy. Neuroimaging modalities may improve the process of identifying neurodegenerative brain changes in RBD at an earlier stage and shed prognostic light on the course of the disease. An increasing number of neuroimaging studies are now available on this topic. However, many studies show variable and conflicting results, probably due to methodological differences and heterogeneity of patient samples.

However, two approaches have provided reproducible results and may indeed be valuable as biomarkers for prodromal disease stages. First, several studies have consistently shown a decrease in presynaptic dopamine levels in iRBD, and a clear association between dopaminergic erosion and subsequent phenoconversion. Decreased striatal uptake of a presynaptic dopaminergic tracer in an individual iRBD patient almost certainly implies imminent phenoconversion. However, predicting the specific type of α-synucleinopathy to which the patient will convert (i.e. PD, DLB, or MSA) with DAT-SPECT or FDOPA-PET alone is still difficult [153]. Secondly, three independent studies have shown that the PDRP is expressed in metabolic PET and perfusion SPECT data of RBD patients. One longitudinal study has confirmed the relationship between PDRP expression and subsequent phenoconversion.

As MRI is a widely available and non-invasive modality, the development of a disease-specific MRI biomarker, sensitive to changes in the prodromal state and conducive to monitoring disease progression and therapeutic intervention, is highly desirable. However, reports from conventional structural MRI, rs-fMRI, DTI, and MRS are still relatively incoherent although there may be some promising approaches within the realm of microstructural, functional, and/or metabolic imaging [53], or a combination of several structural markers.

Sufficient longitudinal data is lacking for almost all imaging techniques. Longitudinal studies are needed to verify the current findings and provide further insights into the pathogenesis of RBD as it progresses to neurodegenerative disease. Combining different imaging modalities may enhance accuracy of prognostic predictions.

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The Electromyographic Diagnosis of REM Sleep Without Atonia and REM Sleep Behavior Disorder

31

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31.1 Definition of RWA/RSWA and Historical Description

In normal conditions, during rapid eye movement (REM) sleep, there is an active inhibition of muscle activity leading to complete or near-complete muscle atonia that can be measured by EMG recording [1]. The failure to inhibit muscle tone during REM sleep results in REM sleep without atonia, commonly referred to with its acronym RWA or RSWA, depicting the polysomnographic (PSG) finding of increased (sustained and/or intermittent) submental electromyographic (EMG) tone during REM sleep.

RWA represents the PSG hallmark of REM sleep behavior disorder (RBD), a parasomnia of REM sleep characterized by absent or greatly diminished atonia during REM sleep, associated with vivid dreams and/or nightmares and prominent motor activity that often appears to be dream-enacting behavior [1, 2].

The first formal description of RBD is to be attributed to Carlos Schenck and colleagues in 1986 [3], in a detailed paper published in SLEEP, in which they described the cases of four elderly men complaining "histories of injuring themselves or their spouses with aggressive behaviors during sleep, often during attempted dream behaviors" and one elderly woman who "had disruptive though nonviolent sleep and dream behaviors." All these patients had undergone a video-PSG (vPSG), with nocturnal behaviors being continuously recorded on videotape, while a technician directly observed the patients and wrote observations on the paper polysomnogram (i.e., before the advent of digital recordings). PSG

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recordings "did document REM sleep pathology with variable loss of chin atonia"; in particular, "In all of these patients, REM sleep was characterized by jerky movements and at times complex behaviors that were clearly inappropriate to the immediate environment; sometimes they could readily be identified as attempted dreams enactments. All the patients demonstrated an extraordinary amount of EMG twitching during REM sleep…Thus sleep laboratory evaluation documented intentional behaviors generated during REM sleep dreams."

Subsequent papers [4–8] describing RBD confirmed the same clinical and vPSG characteristics described by Schenck et al. in 1986 [3].

Despite the crucial relevance of RWA for the diagnosis of RBD, the current ICSD-3 criteria do not establish cutoff values for abnormal atonia during REM sleep, although "the most current evidence-based data that are in accordance with AASM 30 s epoch scoring guidelines should be utilized"[9]. In this context, the ICSD-3 lists the following evidence-based cutoff by the Sleep Innsbruck-Barcelona (SINBAR) group (as a guideline): "Any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in >27% of REM sleep, scored in 30 s epochs." Before 2006 only a few systematic studies quantitatively analyzed chin muscle EMG activity during REM sleep, with the aim to exactly quantify REM sleep atonia and REM sleep phasic muscle activity [10–13]. Most of these early methodologic studies will now be described.

The Bliwise and Rye group developed a visual scoring system for short-duration (approximately 100-ms) phasic EMG activity recorded from five different muscle groups (submentalis, left/right anterior tibialis, left/right brachioradialis) recorded from two different age groups of normal subjects and a group of patients with Parkinson's disease (PD) [11]. Quantification of this activity was labeled as a "phasic EMG metric (PEM)." PEM data were separately analyzed for REM and NREM sleep. PEM was found to be a normal part of REM sleep in all muscle groups and comprised about 5% of 2.5-s intervals of REM sleep in the mentalis muscle of healthy young adults. PEM occurred at higher rates in patients with PD, and its quantification in the legs may be influenced to some extent by the presence of PLMS. Therefore, PEM was found to be a useful metric for adaptation to quantitative digital techniques, with particular relevance for the early detection of neurodegenerative disorders in which disinhibition of midbrain dopaminergic pathways results in excessive motor discharge during sleep.

Bliwise and Rye then conducted a controlled follow-up study to determine the validity of the PEM in identifying patients with RBD [14]. PEM was quantified as the % of 2.5-s intervals with phasic muscle activity of 100-ms duration with an amplitude of at least 4 times background activity in 11 RBD patients and 31 controls. Data were derived from both REM and NREM sleep from five muscle groups (mentalis, left/right anterior tibialis, left/right brachioradialis). Relative to controls, RBD patients had significantly higher levels of PEM activity in all recordings. The largest differences occurred during REM sleep for the mentalis and brachioradialis channels. The authors commented that PEM may be a useful metric to characterize REM sleep-related phasic muscle activity in patients with a history suggestive of RBD, even when no behaviors during REM sleep are detected during video-PSG.

Eisensehr et al. developed a method for assessing long-lasting EMG activity during REM sleep lasting persistently longer than 0.5 s in 8 patients with idiopathic subclinical RBD, 8 patients with idiopathic clinical RBD, 8 patients with PD stage Hoehn and Yahr I, and 11 controls [15]. Long-lasting EMG activity was found to be independently associated with reduction of striatal dopamine transporters as determined by SPECT—with a progressive correlation across a continuum of patients such as idiopathic subclinical RBD, iRBD, and PD (controls had no abnormalities).

The first and the most widely accepted visual scoring method for detecting RWA was developed by Lapierre and Montplaisir (Montréal method) in 1992 [13]. Subsequently, other research groups [14–17] introduced their visual/manual RWA scoring methods, and, among these, the most used are the SINBAR method, developed in 2008 by the Barcelona and Innsbruck groups [16, 18–20], and the McCarter and St. Louis (adapted) method from the Mayo Center for Sleep Medicine, developed in 2014 [17], which was based on the SINBAR method and with the phasic bust duration based on the Bliwise and Rye method [11, 14].

These visual and manual scoring methods have been validated only in relatively small cohorts of subjects, are time-consuming, require to be performed by an expert clinician, and replicability of the performance in independent labs might be lower [21].

For these reasons, in order to obtain a more rapid and reproducible scoring method, an automatic scoring algorithm was introduced in 2008, also known as REM sleep atonia index (RAI) [22], which was later improved with the introduction of a noise-reduction procedure and was followed by the introduction of cutoff values for normal REM atonia [23].

Some other research groups developed other automatic scoring methods, such as the STREAM method by Burns et al. in 2007 [24], the REMREEA algorithm by *Zhang* et al. in 2008 [25], th*e method* by Kempfner et al. in 2010 [26], the SINBAR group in 2014 introduced a computer-assisted scoring algorithm for RWA detection [27], using their criteria published in *2012* [19], and *finally* the method by Frandsen et al. in 2015 [28].

31.2 Polygraphic Features of RWA/RSWA

The latest version of "The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications" [29] distinguishes between sustained muscle activity (tonic activity) in REM sleep in the submental muscle EMG and excessive transient muscle activity (phasic activity) during REM in the submental muscle or limb EMG but does not provide quantitative indications on how many tonic or phasic epochs are needed to define RWA.

In the *International Classification of Sleep Disorders* 3rd edition [9], the diagnostic criteria for RBD refer directly to the AASM Manual for the assessment of RSWA and indicate that "RBD is associated with EMG abnormalities during REM

sleep. The EMG demonstrates an excess of muscle tone during REM sleep, and/or an excess of phasic EMG/twitch activity during REM sleep," again without any well-established threshold of normal EMG tone that might be helpful in grading loss of normal REM atonia.

The features of chin EMG vary across each sleep stage [29]. During wakefulness its amplitude changes continuously, but it is usually higher than during sleep stages [29]. During sleep stage N1, the chin EMG amplitude is variable, but often lower than in wakefulness. As sleep becomes deeper, the amplitude of the chin EMG is variable, but it usually decreases: in stage N2 it is usually lower than in wakefulness and stage N1, and in sleep stage N3, it is often lower than in stage N2; in both stages N2 and N3, it may sometimes be as low as in REM sleep [29]. In normal conditions, during REM sleep there is an active inhibition of the muscle activity, leading to a complete or near-complete loss of activity recorded with surface EMG derivations; consequently, the baseline EMG activity in the chin derivation is no higher than in any other sleep stage and is usually at the lowest level of the entire recording [29].

When the mechanisms of the active inhibition of muscle activity are altered, EMG recordings during REM sleep are characterized by electrophysiological findings of excessive amounts of sustained or intermittent elevation of the submental EMG tone and/or excessive transient muscle activity on the submental or limb derivations, namely, RWA [1].

According to the AASM scoring manual [29], as also reported in the ICSD-3 [9], RSWA can be scored when there is *sustained muscle activity (tonic activity*) in REM sleep with at least 50% of the duration of the epoch having a chin EMG amplitude greater than the minimum amplitude demonstrated in NREM sleep and/or *excessive transient muscle activity (phasic activity)* in REM sleep with at least five (50%) mini-epochs (a 30-s epoch is divided into ten 3-s mini-epochs) containing bursts of transient muscle activity. Excessive transient muscle activity bursts are 0.1–5.0 s in duration and at least four times as high in amplitude as the background EMG activity.

Figure 31.1 shows, as examples, two epochs of REM sleep recorded in a patient with RBD showing excessive chin muscle tone and excessive phasic EMG/twitch activity over the chin, tibialis anterior, and flexor digitorum superficialis muscles (panel A); panel B reports an example of excessive muscle tone and excessive phasic EMG activity over the chin (only sporadic small bursts of activity are recorded from the flexor digitorum superficialis muscles).

31.3 Visual and Automatic Scoring of Atonia During Normal and Pathological REM Sleep

31.3.1 The Montréal Method (Lapierre and Montplaisir)

As introduced above, in 1992, in a pioneering work, Lapierre and Montplaisir [13] were the first authors to propose a systematic manual method for the scoring of REM atonia based on submentalis muscle tone, the so-called Montréal method. It

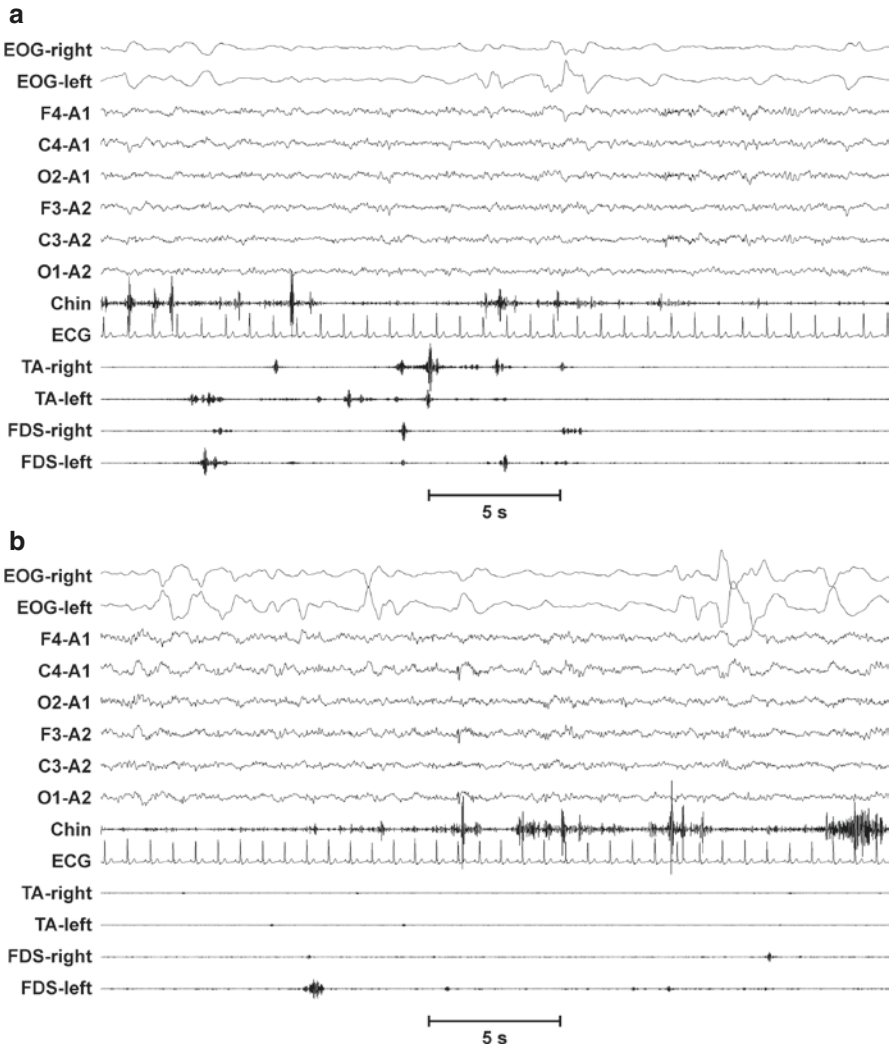

Fig. 31.1 REM sleep recorded in a patient with RBD. Panel (**a**): excessive chin muscle tone and excessive phasic EMG/twitch activity over the chin, tibialis anterior, and flexor digitorum superficialis muscles. Panel (**b**): excessive muscle tone and excessive phasic EMG activity over the chin with only sporadic small bursts of activity recorded from the flexor digitorum superficialis muscles. *EOG* electrooculogram, *ECG* electrocardiogram, *TA* tibialis anterior muscle, *FDS* flexor digitorum superficialis muscle

should be noted, however, that as indicated in the title of their paper, this was a first effort for the development of a scoring method in RBD, and the sample size was very small, with five idiopathic RBD patients and five controls.

However, before assessing the degree of RWA, these authors needed to define the criteria to score REM sleep in recordings in which it lacks one of its fundamental

components (i.e., muscle atonia). Thus, Lapierre and Montplaisir [13] modified the Rechtschaffen and Kales criteria [30] used at that time as follows: the onset of a REM sleep period corresponds to the first REM; the end of a REM sleep period is identified by the occurrence of an EEG feature characteristic of another sleep stage (viz., sleep spindles, K-complexes, slow waves) or the occurrence of an EEG arousal or by the absence of REMs for at least three consecutive minutes. It is important to note that these modifications have not been proposed or tested for the current AASM criteria [29] for scoring sleep stages; this makes the current AASM criteria unsuitable for scoring sleep in RBD and represents an unresolved problem with these criteria. For this reason, until an agreement is reached in the scientific community, it is advisable to use the previous Rechtschaffen and Kales criteria [30] with the modifications introduced by Lapierre and Montplaisir [13], adapted to 30-s long epochs for scoring sleep in RBD. Moreover, the same criteria should be used for scoring sleep in controls or other groups when a comparison is needed with RBD subjects. This has only rarely been clearly reported in the literature, so far.

The Montréal method indicates to score each REM sleep epoch as tonic or atonic based on the amplitude of the submental muscle EMG activity. Two different types of chin muscle activities were proposed: "phasic" and "tonic." With this method, an epoch is defined as "tonic" if the amplitude of chin EMG is at least twice than the background EMG or greater than 10 μV and lasting longer than 50% of the epoch; the "phasic" activity has an amplitude greater than four times the background EMG and lasts 0.1–5 s. Other parameters correlated to REM sleep, identified by the Montréal method, are phasic chin EMG density and REM density. "Phasic chin EMG density" is scored as the percentage of 2-s mini-epochs containing EMG activation lasting 0.1–10 s, with amplitude four times greater than the amplitude of the background EMG activity. The phasic EMG activity is present in epochs of REM sleep that are scored either as tonic or atonic. "The REM density" is calculated as the percentage of 2-s mini-epochs containing at least one REM.

Lapierre and Montplaisir also considered leg movements (LM) recorded from both anterior tibialis muscles. Both LM during sleep index (LMSi) and periodic LM during sleep index (PLMSi) were calculated separately in NREM and REM sleep. This method was subsequently validated in 2010 by Montplaisir and colleagues, who identified the cutoff values to be used for the diagnosis of RBD [31]. A reanalysis of the same set of recordings demonstrated the validity of the method also when it is applied to 30-s epochs [32].

Consens et al. sought to validate, in a larger group of RBD patients with two consecutive PSG studies, the Lapierre and Montplaisir method—which they noted was based on a comparison of five RBD patients and five controls during one PSG study [12]. Patients with neurodegenerative disorders considered to be at risk for RBD were clinically evaluated and underwent two consecutive PSG studies. Two different PSG RBD scores were generated: the % of 30-s REM sleep epochs with at least 15 s of tonically maintained EMG activity and the % of 3-s REM sleep mini-epochs that contained phasic EMG bursts. The results found that the tonic and phasic EMG measures, when combined, were significantly higher in patients with probable or possible RBD (n = 9) than in patients judged unlikely to have RBD (n = 4). The overall PSG measure significantly correlated with symptom scores, and specific PSG RBD measures on night 1 correlated highly with those on night 2. This

quantitative method to assess the severity of RBD PSG features was found to be both valid and reliable in patients at risk for RBD on account of having neurodegenerative disorders.

31.3.2 The SINBAR Method

Based on the results of two preliminary studies for the evaluation of the set of muscles that were most activated during REM sleep in RBD [16, 18], the SINBAR group proposed a manual and visual scoring method for RWA, comparing RWA assessed in 11 different muscles and in different combinations. The authors found in 30 patients and 30 controls that using a montage including a combination of submentalis EMG and bilateral flexor digitorum superficialis (FDS) EMG [19], findings from RBD patients differed significantly from control subjects, with a very high sensitivity and specificity and better than the classic montage that included only the submentalis and anterior tibialis muscles [16, 18–20]. Therefore, they recommended that in every RBD patient, the routine EMG montage should include bilateral flexor digitorum superficialis EMG or upper extremity EMG. (The calculations in this study were made not only for these final recommended muscle combinations but also for multiple other isolated muscles or combinations and for 3- and 30-s time windows [19]. Also, cutoffs for the combinations of EMG channels were included among values for individual and different types of other EMG combinations. The authors discussed that these values were made available because in many laboratories EMG montages of the upper extremities were not utilized [19]).

This recommendation was reinforced by a recent study from the Barcelona group that compared two EMG montages, viz., isolated mentalis muscle vs. mentalis muscle, in combination with upper limb muscles (biceps brachii or flexor digitorum superficialis) in initial diagnostic vPSG of 49 patients with iRBD who eventually converted to overt neurodegenerative disease, quantification of EMG activity in the upper limbs combined with the mentalis increased the diagnostic sensitivity iRBD compared to the isolated measurement of the mentalis [33]. Normal EMG values were found in the mentalis muscles of 18.3% of patients, but all were correctly diagnosed with RBD after audio-visual analysis of behaviors (or with additional EMG from flexor digitorum superficialis muscles in all patients, or biceps muscles in most patients). PSG time-synchronized audiovisual analysis showed abnormal REM sleep behaviors in all nine patients with values below the established cutoff values. The authors concluded that quantification of EMG activity in the upper limbs combined with the mentalis increases the ability to diagnose RBD when compared with the isolated measurement of the mentalis, and that detection of typical abnormal behaviors during REM sleep with audiovisual analysis is essential for the diagnosis of RBD in patients with EMG values below the published cutoffs.

With the SINBAR method, phasic EMG activity is defined as any burst of EMG activity lasting 0.1–5 s with amplitude more than twice the background EMG activity. Each REM epoch is divided in 3-s mini-epochs, and each mini-epoch is scored as having or not having EMG activity; the percentage of 3-s mini-epochs containing phasic EMG activity, out of the total number of REM sleep mini-epochs, is calculated. The percentage of 3-s mini-epochs containing phasic chin EMG activity as

well as "any" chin EMG activity, out of the total REM sleep mini-epochs, is also calculated along with the percentage of 3-s mini-epochs with "any chin EMG activity combined with bilateral phasic FDS EMG activity" out of the total REM sleep 3-s mini-epochs. The percentage of 30-s epochs containing five or more 3-s mini-epochs with "any chin EMG activity combined with bilateral phasic FDS EMG activity" out of the total REM sleep epochs is also calculated. Finally, each REM sleep 30-s epoch is scored as "tonic" when the increased EMG activity is present in more than 50% of the epoch, with amplitude at least twice the background EMG or more than 10 μV.

The SINBAR group identified the following cutoff values with the best specificity and sensitivity: >16.3% of 3-s mini-epochs with phasic chin EMG activity, >18% of 3-s mini-epochs with any chin EMG activity, >32% of 3-s mini-epochs with any chin EMG activity combined with bilateral phasic EMG activity in the FDS, and >27% of 30-s epochs with any chin EMG activity combined with bilateral phasic EMG activity in the FDS. In contrast, cutoffs for the combination of mentalis and both tibial anterior muscles was 46.4% for the 3 sec mini-epochs and 45.5% for the AASM recommended 30 sec epochs [19].

31.3.3 The McCarter and St. Louis Method (Adapted from the SINBAR and Bliwise-Rye Methods)

In 2014 McCarter and colleagues, from the Mayo Center for Sleep Medicine, proposed a visual and manual method for quantifying REM sleep EMG activity [17], which was adapted from previously established methods [11, 14, 19], including the combination of chin and anterior tibialis muscles. The aim of their study was to evaluate if phasic burst duration and RWA methods could accurately differentiate RBD patients from those with OSA. They identified 20 patients with Parkinson's disease and RBD (PD-RBD), 20 patients were primary snorers, and 20 patients were affected by OSA without history of dream enactment. Each subject underwent to a complete vPSG recording, including EMG recording of the submentalis (SM) and bilateral anterior tibialis (AT) muscles.

In all patients the background EMG tone during REM sleep was identified; it ranged between 0.5 and 2 μV. The phasic, tonic, and "any" (tonic, phasic, or both forms occurring in the same 3-s mini-epoch) muscle activity during REM sleep were visually determined and manually scored. Both phasic and "any" percent muscle activity were calculated separately for SM and AT muscles; moreover, the duration of each phasic muscle burst was individually measured.

Each 30-s epoch was scored as "tonic" when at least 50% of the epoch contained sustained activity greater than twice the background EMG or was ≥10 μV. The percentage of tonic activity was calculated as the total number of positive 30-s epochs divided by the total number of 30-s REM epochs.

Furthermore, each 30-s epoch was divided into 3-s mini-epochs for analysis of "phasic" and "any" activity in both AT and SM muscles; phasic activity of EDC was scored only in RBD patients. A 3-s mini-epoch was scored as positive for phasic activity when a phasic EMG burst was present. A phasic EMG activity was

considered a "burst" if measured more than four times the background amplitude and lasting 0.1–14.9 s. The end of a phasic burst corresponds to the return of muscle activity to baseline for at least 200 ms.

A 3-s mini-epoch was scored as positive for "any" muscle activity when it contained either tonic or phasic activity in either SM or AT muscles or both.

Mini-epochs containing a breathing event or an arousal were excluded and classified as "artifact."

Overall phasic and "any" percent muscle activity was calculated as the total number of positive 3-s mini-epochs divided by the total number of analyzable 3-s mini-epochs. For the combined analysis, a 3-s mini-epoch was considered positive if there was phasic or "any" EMG activity in either the SM or AT muscles and negative if there was an absence of EMG activity in both muscles.

The authors provided the following thresholds for the definition of RWA, with respect to the total number of REM sleep 3-s mini-epochs: 15.5% for phasic and 21.6% for any activity in the SM muscle, 30.2% in the AT muscles for both (phasic or any activity), and 37.9% for phasic or 43.4% for any activity, when SM and AT muscles were combined.

Furthermore, diagnostic cutoffs for 3-s epochs (AASM criteria) were 2.8% for the SM muscle, 11.3% for the AT muscles, and 34.7% for the combined SM and AT muscles. A tonic muscle activity of 1.2% was found to be 100% sensitive and specific for the diagnosis of RBD, while RAI (SM) cutoff was indicated to be 0.88. Finally, muscle burst duration cutoffs were 0.65 s for the SM muscle and 0.79 s for the AT muscles. According to these authors, the combination of phasic burst duration with RWA muscle activity improves both sensitivity and specificity of RBD diagnosis.

However, notably even their subsequent 2017 paper, the McCarter-St. Louis group found that the anterior tibialis muscle was the least specific and least sensitive muscle for RBD diagnosis [34], which replicated the SINBAR findings [16, 19], which is why SINBAR introduced upper extremity EMG recordings to enhance specificity and sensitivity for RBD diagnosis. The original contribution in the McCarter-St. Louis method was the additional use of phasic EMG burst duration that was originally developed and expanded by the Bliwise-Rye group regarding the phasic burst duration—PEM (phasic EMG metric) [11, 14, 35, 36].

31.3.4 Computer-Based Automatic Scoring of RWA/RSWA

The manual-visual scoring of atonia during REM sleep is time-consuming and must be carried out by expert scorers; moreover, all the above methods have been validated only in relatively small cohorts of subjects. For these reasons in 2008, a group of Italian scientists developed an automatic algorithm for scoring RSWA that was based on a strictly quantitative evaluation of the amplitude of the SM muscle EMG [22].

They enrolled not only patients with idiopathic RBD but also with multisystem atrophy (MSA), along with age-matched and young normal controls. The SM EMG signal was digitally band-pass filtered and rectified; the EMG signal was subdivided

into 1-s mini-epochs, and then for each mini-epoch, the average amplitude of the rectified SM muscle EMG signal was obtained.

The authors observed that during clear-cut REM sleep atonia, the average mini-epoch amplitude of the SM muscle EMG was usually ≤1 μV; conversely when phasic or tonic muscle activations were visually clearly detectable in the unrectified signal, the average mini-epoch EMG amplitude was consistently >2 μV. The values of the SM muscle EMG signal amplitude in each mini-epoch were used for a detailed analysis of their statistical distribution properties. On this basis, the authors introduced an index of preponderance of the amount of mini-epochs with average EMG amplitude ≤1 μV over the total number of mini-epochs during REM sleep (with the exclusion from the count of those with amplitude >1 ≤ 2 μV), in order to obtain a single value: the REM sleep atonia index (RAI). The range of RAI varies between 0 (absence of mini-epochs with amp ≤1 μV, indicative of complete absence of atonia) and 1 (all mini-epochs with amp ≤1 μV, corresponding to complete atonia).

This method was improved by the same group of authors in 2010 [23], by introducing a simple noise reduction procedure, before the calculation of RAI. Three empirical ranges were then set at RAI <0.8, 0.8 ≤ RAI <0.9, and RAI ≥0.9. All young normal controls showed RAI ≥0.9; conversely 74.4% of all iRBD showed RAI <0.9, with 38.5% of the whole group having RAI <0.8 and only 25.6% with RAI ≥0.9; all MSA patients showed RAI <0.8. After noise reduction, RAI values <0.8 are considered to be indicative of definitely altered (reduced) EMG atonia, while values between 0.8 and 0.9 might indicate a less evident (mild) alteration of atonia, and values ≥0.9 are indicative of normal atonia.

The value of this method in the diagnosis of RBD has been investigated by comparing it to the visual scoring method for RWA [21, 32]. The accuracy of the diagnosis of RBD was reported to be high with both visual and automatic methods, and there was a high concordance between the methods, concluding that the automatic algorithm should be used as the first-line process in detecting RWA together with visual evaluation of video recordings, reserving the use of the manual scoring methods to equivocal cases.

Finally, as introduced above, the SINBAR method has been implemented in an automatic detection approach of phasic, tonic, and "any" EMG activities, mimicking the visual approach, also in order to overcome the time-consuming visual procedure [27].

Table 31.1 reports a summary of the features of the four methods to measure REM sleep muscle atonia presented in this chapter.

31.4 Isolated RWA/RSWA or Subclinical RBD?

The introduction of quantitative (visual and automatic) methods for the assessment of RSWA has soon disclosed the existence of subjects with isolated RWA (without RBD). Montplaisir et al. [31], in the validation study for the Montréal method, noticed that approximately 10–12% of their controls had high values in at least one of their measures of the chin EMG amplitude. Also the automated RAI has reported decreased atonia in a few normal controls [22, 23, 37], particularly in the oldest

Table 31.1 Summary of the four methods to measure REM sleep muscle atonia presented in this chapter with selected diagnostic cutoff values

Method	Explored muscles	Patients	Epoch length	Mini-epoch length	Threshold for RSWA in RBD diagnosis
Montréal (*Lapierre and Montplaisir, 1992*) [13]	Chin, anterior tibialis	5 RBD	20 s	2 s	• Tonic REM epochs ≥30% of total REM epochs (with chin EMG at least twice than background or >10 μV)
		5 normal controls	(30 s)	(3 s)	• Phasic REM mini-epochs ≥15% of total REM mini-epochs (with chin EMG four times greater than baseline)
		7 controls with PLMS			• Tonic EMG + phasic EMG
					• Leg movements in REM ≥24/h
					• REM density (percentage of 2-s mini-epochs with ≥1 REM)
SINBAR (*Frauscher* et al., *2012*) [19]	Chin, bilateral flexor digitorum superficialis, sternocleidomastoid, biceps brachii, anterior tibialis, and extensor digitorum brevis	15 iRBD	30 s	3 s	• >27% of REM epochs with any chin EMG activity and/or phasic EMG activity in the FDS
		15 PD-RBD			• >16.3% of REM mini-epochs with phasic chin EMG activity
		30 normal controls			• >18% of REM mini-epochs with any chin EMG activity
					• >32% of REM mini-epochs with any chin EMG activity and/or phasic EMG activity in the FDS

(continued)

Table 31.1 (continued)

Method	Explored muscles	Patients	Epoch length	Mini-epoch length	Threshold for RSWA in RBD diagnosis
Mayo Clinic (*McCarter* et al., *2014*) [17]	Chin, anterior tibialis	20 PD-RBD	30 s	3 s	• Chin "any" 21.6%
		20 normal controls			• Chin phasic 15.5%
		20 OSA			• AT "any" 30.2%
					• AT phasic 30.2%
					• Chin + AT "any" 43.4%
					• Chin + AT phasic 37.8%
					• Chin + AT tonic 1.2%
REM sleep atonia index (*Ferri et al., 2010*) [23]	Chin	25 young controls		1 s	• RAI <0.8 = definitely abnormal atonia
		10 aged controls			• RAI 0.8–0.9 = mildly abnormal atonia
		31 untreated iRBD			• RAI >0.9 = normal atonia
		8 treated iRBD			
		10 MSA			
		5 OSA			

RSWA REM sleep without atonia, *RBD* REM sleep behavioral disorder, *iRBD* idiopathic REM sleep behavioral disorder, *PD* Parkinson's disease, *MSA* multiple system atrophy, *OSA* obstructive sleep apnea, *FDS* Flexor digitorum superficialis, *AT* Anterior tibialis

subjects [38]. Sasai et al. [39], in a retrospective study specifically arranged to detect isolated RWA, were able to identify some subjects without RBD who had "incidental" RWA with atonia measures falling above the thresholds established by the SINBAR group [19] for the diagnosis of RBD.

It is not clear yet whether subjects without RBD but with RWA are at risk of developing RBD or not. Data available so far are still preliminary but indicate the need to further investigate this topic [39, 40]. In one study, there was a continuous increase in EMG activity in REM sleep over time [40].

This is an important but still unresolved issue because of its potential prognostic value. An isolated RWA that does not evolve to RBD might indicate that mechanisms different from those indicated for RBD [41] may cause the appearance of abnormal EMG activity during REM sleep. This is certainly possible because, as an example, isolated RWA has been found in some patients with amyotrophic lateral sclerosis, which was believed to be probably a genuine effect of the pathology per se, correlated with the degree of severity of the disease [42].

On the other hand, isolated RWA might indicate the existence of a condition of "subclinical" RBD. The term subclinical RWA has been used in a non-univocal way to refer either to the observation of dream enactment behaviors in subjects in whom RBD could not be diagnosed for different reasons or to subjects with the abovementioned "incidental" RWA [39, 40, 42].

However, the term "subclinical RBD" has been used also for patients developing fully expressed RBD after long-standing subclinical behavioral manifestations during sleep, consisting of chronic, often progressively more frequent and/or intense, limb jerking and twitching [7]. This group of subjects should not be confused with that with isolated RSWA, at least on the basis of the current knowledge.

It is not known if a genetic background characterizes RWA, but it might be interesting to investigate the eventual presence of such a background because it might be speculated that RWA may be considered to be an endophenotype of RBD, similarly to the increasingly clearer links between periodic leg movements during sleep and restless legs syndrome [43].

Finally, the automated quantitative analysis of tonic and phasic muscle activity in RBD developed by Mayer et al. deserves mention [44]. Their automatic analysis allowed for the quantification of muscle activity and its amplitude for all sleep stages, with a focus on REM sleep in patients with RBD. Forty-eight patients (27 male, 21 female) with RBD were included in the analysis. The study included 21 patients with iRBD, 28 with RBD-narcolepsy, and 25 controls without confirmed sleep disorder. The amplitude of the EMG was generated from the difference of the upper and lower envelope of the mentalis muscle recordings. By smoothing the amplitude curve, a threshold curve was defined, with muscle activity beyond the threshold curve being defined as motor activity. The means of the motor activity/s were summated statistically and calculated for each sleep stage. Due to the variable distribution of REM sleep, the latter was assigned to respective quartiles of the recorded night. Muscle activity was defined according to a histogram as short-lasting (<0.5 s) and long-lasting (>0.5 s) activity. No difference in the distribution of REM sleep/quartile and mean muscle tone throughout the sleep cycle could be found within the RBD groups and control subjects. Muscle activity was in the range of 200 ms. No clusters or regular distribution of muscle activity was found. Long muscle activity in the group with manifest clinical RBD was significantly higher than in control subjects, whereas it was not significantly higher in subclinical RBD. The correlation between the frequency of long muscle activity in REM sleep and age was highly significant only for patients with idiopathic RBD. Therefore, automatic analysis of muscle activity in sleep was found to be a reliable, easy method that may easily be used in the evaluation for REM sleep behavior disorder, creating indices of muscle activity similar to the indices for sleep apnea or PLMs. Long-lasting movements in REM sleep appear to represent motor disinhibition found in RBD that is more distinct than short-lasting movements.

31.5 The Role of REM Sleep Without Atonia in the Diagnosis of REM Sleep Behavior Disorder: New Challenges

The current ICSD-3 criteria for the diagnosis of RBD [9] require a polysomnographic demonstration of RSWA; however, in a note, they also state that "On occasion, there may be patients with a typical clinical history of RBD with dream-enacting behaviors, who also exhibit typical RBD behaviors during video-PSG, but do not demonstrate sufficient RWA, based on the current evidence-based data, to satisfy the PSG criteria for diagnosing RBD. In such patients, RBD may be provisionally diagnosed, based on clinical judgment. The same rule applies when video-PSG is not readily available."

Thus, with the current rules in the ICSD-3 [9], patients with a history dream enactment strongly suggestive of RBD but without diagnostically sufficient RSWA can be diagnosed as having RBD provided that there is a definitive episode of dream enactment during REM sleep (viz., a RBD episode) recorded by vPSG; and subjects who do exhibit RSWA but do not show behavioral episodes can be considered to not have clinical RBD. Therefore, RSWA and RBD can occur independently from each other, and there is certainly a "gray zone" into which both RBD patients and normal controls can fall, under certain circumstances. The causes of this gray zone might be methodological or biological.

From the methodological point of view, the measurement of RSWA with any of the approaches proposed so far has the problems that usually affect measures for which thresholds need to be established; from this point of view, only few papers have been published with relatively large numbers of patients and controls, and the figures of sensitivity and specificity for the thresholds obtained in one study have not usually been validated by independent analyses. Not even the supposed advantages of adding upper limb EMG derivations [33] have been clearly confirmed by independent analyses carried out by research groups different from the team that introduced this addition [21].

Among the biological factors, the night-to-night variability of the measurement of RWA is a well-known phenomenon [45, 46], and it is not clear if the repetition of the recording for a second night can be considered to be cost-effective [45, 46]. A semi-automated scoring algorithm for REM sleep muscle activity has been developed that awaits further testing [47]. As seen above, the presence of a comorbid condition, such as amyotrophic lateral sclerosis, for example, might be correlated with the detection of RSWA which, in turn, might have a different basal mechanism [42]. Finally, another very important biological factor is age because REM sleep muscle atonia changes continuously from the infantile period to elderly, with complex and differential modifications of REM atonia and "phasic" EMG activities during REM sleep [38].

In conclusion, the role of RWA in the diagnosis of RBD is certainly central but not absolute, and an appropriate clinical judgment should guide the diagnostic process.

Note Added in Proof: Four pertinent studies have recently been published: (1) Guttowski D, Mayer G, Oertel WH, Kesper K, Rosenberg T. Validation of semiautomatic scoring of REM sleep

without atonia in patients with RBD. Sleep Med. 2018; 46:107–13. (2) Cesari M, Christensen JAE, Kempfner L, et al. Comparison of computerized methods for REM sleep without atonia detection. Sleep. 2018 Jul 13. https://doi.org/10.1093/sleep/zsy133. (3) Bliwise DL, Fairley J, Hoff S, Rosenberg RS, Rye DB, Schulman DA, Trotti LM. Inter-rater agreement for visual discrimination of phasic and tonic electromyographic activity in sleep. Sleep. 2018. https://doi.org/10.1093/sleep/zsy080. (4) Olesen AN, Cesari M, Christensen JAE, Sorensen HBD, Mignot E, Jennum P. A comparative study of methods for automatic detection of rapid eye movement abnormal muscular activity in narcolepsy. Sleep Med. 2018;44:97–105.

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RBD and the Autonomic Nervous System

32

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32.1 Blood Pressure Regulation

32.1.1 Orthostatic Hypotension and Systolic Blood Pressure Dysregulation in Parkinson's Disease

Orthostatic hypotension (OH) is defined as a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic when standing or during head-up tilt test. Prevalence of OH increases with age; 5–30% of general elderly population (65 years or older) showed OH [1–3]. The incidence is remarkably high in Parkinson's disease (PD) patients; either population-based or clinical cohort-based studies noted that almost half of PD patients had OH [4–6]. In PD patients, baroreflex-mediated sympathetic activation, which causes vasoconstriction to maintain blood pressure when standing, is absent or attenuated resulting in OH [7]. OH occurs early in or occasionally precedes PD. In a study of 35 PD patients, 21 (60%) of PD patients had OH before, concurrent with, or within 1 year after the onset of PD, of whom OH had preceded parkinsonism in 4 (11%) patients [8]. PD patients also have more remarkable systolic blood pressure drop compared to idiopathic RBD patients: more significant in PD patients with RBD than in those without RBD [9, 10].

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32.1.2 Orthostatic Symptoms and Hypotension in Idiopathic RBD

In idiopathic RBD patients, systolic blood pressure drop was larger compared to controls, and the level of blood pressure drop was significantly greater in patients who developed PD compared to those did not [9, 11]. Idiopathic RBD patients also show an intermediate level of blood pressure regulation during an orthostatic standing test, between PD and controls [12]. Some prior studies failed to show difference in orthostatic symptoms evaluated by means of MSA rating scale or SCOPA-AUT between idiopathic RBD irrespective of the development of PD/DLB and controls [11, 13]. However, in a large-scale multicenter study, idiopathic RBD patients show higher scores in items for cardiovascular problems (light-headed standing up or syncope) [14]. Thus, although not as remarkable as in PD, idiopathic RBD patients have orthostatic symptoms and hypotension. In individuals with isolated rapid eye movement sleep without atonia (without RBD symptoms), the polysomnographic hallmark and a precursor of RBD, OH was not observed after 8.6 ± 0.9 years follow-up even in subjects who showed isolated RWA above optimal diagnostic cutoff [15]. This finding indicates the heterogeneity of RBD pathology; OH is not associated with the extent to which the pedunculopontine tegmental nucleus is impaired. Furthermore, in a prior large cohort study, OH did not predict future development of PD: percentage of patients who had OH at baseline was identical between patients who developed PD and those who did not (18% vs. 17.9%) [16].

32.2 Cardiac Autonomic Dysfunction

32.2.1 Impaired Heart Rate Variability in Idiopathic REM Sleep Behavior Disorder

RBD heralds the onset of Lewy body diseases [17], which represents stage 2 of the neuropathological process of Parkinson's disease (PD) involving the locus coeruleus [18]. In the Braak hypothesis, cardiac autonomic dysfunction represents an early manifestation of neurodegenerative process involving brain stem area as stage 1 of the disease course. A number of prior studies noted cardiac sympathetic denervation in Lewy body diseases [19–22], which occurs earlier than orthostatic hypotension [21]. In idiopathic RBD, cardiac autonomic dysfunction is widely observable.

In patients with idiopathic RBD, cardiac autonomic dysfunction is highly recognized during both wakefulness and sleep. In the first report, 64% of idiopathic RBD patients showed abnormal results in cardiovascular autonomic tests during wakefulness (i.e., R-R interval variation, Valsalva ratio, and heart rate response to standing). Moreover, they had a reduced tonic and phasic heart rate (HR) variability (HRV) during sleep (i.e., tonic HR decrease induced by sleep mainly due to vagal activity and phasic HR increase induced by body movement mainly due to sympathetic activity) [23]. Starting with their first notion, cardiac autonomic dysfunction in idiopathic RBD has been confirmed as an early manifestation of an underlying central

nervous system degenerative process associated with Lewy body diseases. In a report conducting spectral analysis of HR during sleep, idiopathic RBD patients showed no REM-related cardiac excitatory response and parasympathetic withdrawal detected as reduced R-R variability, LF/HF ratio, or respiratory frequency [24]. During wakefulness, idiopathic RBD patients showed reduced time- and frequency-domain measures of HRV. Namely, idiopathic RBD patients showed significant reduction in standard deviation of normal R-R intervals (SDNN) which indicates diminished overall HRV, decrease in RMSSD or pNN50 as indicators of abnormality of parasympathetic innervation, and lower LF or VLF spectrum power related to sympathetic inactivity compared to controls [25–27]. Dahms et al. measured autonomic symptoms and central and peripheral autonomic markers in idiopathic RBD and controls [28]. They demonstrated that subjects with idiopathic RBD showed lower HRV and blood pressure variability, indicating peripheral cardiac/vascular denervation, although neither the markers reflecting central autonomic degeneration nor clinical autonomic symptoms in SCOPA-AUT questionnaire differed between cases and controls. Autonomic cardiac/vascular dysfunction arisen from peripheral autonomic degeneration is already detectable prior to the clinical appearance in prodromal α-synucleinopathy and is worth to be evaluated to identify patients with idiopathic RBD.

Regarding HR response to periodic leg movements during sleep (PLMS), which is frequently comorbid with RBD [29], Fantini et al. demonstrated reduced amplitude of cardiac activation detected as heart rate change associated with PLMS compared with restless legs syndrome [27, 30]. Likewise, idiopathic RBD patients showed lower heart rate response to arousals than controls [27]. Thus, cardiac autonomic dysfunction detected as impaired HRV revealed by routine electrocardiograms is useful to discriminate idiopathic RBD from controls. On the other hand, as for RBD motor events, a recent study has shown that idiopathic RBD patients present an increase in HR response to complex motor events compared to elementary ones [31]. In their report, 5 out of 14 RBD patients (seven idiopathic cases and seven PD-RBD cases) showed a difference in HR response according to the complexity of ME. Additionally, PD was more frequent in the responders (four out of five). Effect of dream content or heterogeneity of disease stage related to persistence of sympathetic response should be considered to conclude the HR response to RBD motor events in RBD (see Chap. 33 on Cardiac Scintigraphy in RBD).

32.2.2 Cardiovagal and Adrenergic Dysfunction in Idiopathic RBD

In the first study that quantified autonomic dysfunction in iRBD, using the composite autonomic severity score, a validated instrument for quantifying autonomic failure, 17 iRBD patients were prospectively enrolled, and a battery of standardized autonomic tests was performed, with findings compared to health controls [32]. At least one mild-to-moderate autonomic deficit was found in 16/17 iRBD patients, predominantly in the cardiovagal and adrenergic domains.

32.2.3 Association with Lewy Body Diseases

In idiopathic RBD, degree of cardiac autonomic dysfunction is intermediate with respect to PD patients and controls [27, 33]. Cardiac autonomic dysfunction especially sympathetic inactivity is more pronounced in PD patients as shown by reduced VLF component during wakefulness than in idiopathic RBD patients [33]. In PD patients, neither HR response to PLM, arousal, nor heart rate variability differs between PD patients with RBD and those without RBD. However, circadian HRV recording revealed that either cardiac sympathetic index (night-to-day ratio of LF spectral component) or cardiac parasympathetic index (the rate of HF spectral component) was higher in patients with PD-RBD than in PD without RBD [34]. These findings suggest a heterogeneity of PD pathology in the extent to which the brain stem is involved.

Does cardiac autonomic dysregulation predict future development of α-synucleinopathy? In the first prospective study by means of R-R variability or HR spectrum, patients with idiopathic RBD showed substantial cardiac autonomic dysfunction (i.e., lower SDNN and decreased VLF, LF, and LF/HF ratio); however, the dysfunction was identical between idiopathic RBD patients who later developed parkinsonism or dementia and those who did not [25]. Later studies also failed to prove lower HRV as an accurate predictor of PD [16, 35]. Given these findings, cardiac autonomic dysfunction itself can be associated with RBD, irrespective of neurodegenerative risk. In other words, the dysfunction observed in idiopathic RBD can neither identify patients who had an increased risk of development to α-synucleinopathies nor distinguish those at risk for the other neurodegenerative disorders. Future large prospective study is needed to ascertain this issue.

32.3 Constipation

It has been widely accepted that abnormally low gastrointestinal motility is the most common autonomic symptom in PD patients, with constipation reported by 80% of the affected patients [36]. Based on this, the prevalence and clinical significance of constipation in RBD patients have been receiving attention in clinical researches of the disorder. A cross-sectional study showed that the positivity for constipation is clearly higher in idiopathic RBD patients than controls [14]. Another study of patients with idiopathic RBD found elevated constipation scores at least 6 years before receiving the diagnosis of PD and have led to estimating that scores deviated from control values about 15 years before PD onset [11]. The apparently long lead time for the development of PD raises the possibility that constipation is not only a risk factor but also a prodromal marker. For this reason, positivity of constipation has been included as an item in the Movement Disorder Society criteria for prodromal Parkinson's disease [37]. However, considering a relatively high prevalence of constipation in the general population (15–20%), positivity for this symptom (especially as an isolated finding) probably has a relatively low specificity and predictive value for PD.

Some studies have found positive α-synuclein staining in colonic biopsy tissue obtained from PD patients [38, 39], despite the relation of the finding to subjective constipation not being analyzed. These studies have raised the question whether α-synuclein immunostaining of colonic tissue becomes a marker for the development of α-synucleinopathy in idiopathic RBD patients. With regard to this, one study assessed α-synuclein immunohistochemistry in colonic biopsies obtained from patients with idiopathic RBD and compared findings to those in healthy controls and PD patients [40]. The study result showed that immunostaining for serine 129-phosphorylated α-synuclein (pSyn) in submucosal nerve fibers or ganglia was found in none of 14 controls but was observed in 4 out of 17 idiopathic RBD patients and 1 out of 19 patients with PD. Thus, pSyn immunostaining of colonic biopsies may become one of the suitable candidates to prospectively study as a prodromal PD marker in idiopathic RBD cohort.

32.4 Sexual Dysfunction

Possibly due to dopaminergic dysfunction, a majority of patients with PD acknowledge sexual dysfunction, including erectile dysfunction, ejaculation problems, and difficulty achieving orgasm. A retrospective analysis of a large cohort of men followed between 1986 and 2002 showed a 3.8-fold increase in the likelihood of developing PD among subjects with erectile dysfunction at baseline [41]. In line with this, Postuma and his colleagues reported that severity of erectile dysfunction may predict conversion from idiopathic RBD to a neurodegenerative disorder during 5 years follow-up period [11]. A cross-sectional study also showed that positivity for erectile problems was significantly higher in idiopathic RBD patients compared with controls [14]. However, erectile dysfunction is relatively common in the general population, particularly among older men. Because of this, specificity of erectile dysfunction as a prodromal marker of PD could remain relatively low.

32.5 Urinary Dysfunction

Urinary symptoms in patients with PD are attributable to loss of the D1 receptor-mediated tonic inhibition of the micturition reflex [42], and several studies have shown that patients who present with urinary complaints were at higher risk of developing PD [43, 44]. With respect to idiopathic RBD, urinary domain score of SCOPA-AUT is significantly higher in affected patients compared with controls [14]. In addition, urinary symptoms were documented in idiopathic RBD patients up to 7 years before conversion to PD, with an extrapolated prodromal interval of 13 years [11]. Positivity for urinary dysfunction has also been included as an item in the Movement Disorder Society criteria for prodromal Parkinson's disease [37]. However, the specificity of this prodromal marker is thought to remain relatively low, as urinary symptoms are common in the elderly population.

32.6 Disturbance in Pupillary Reactivity

De novo PD patients have been reported to exhibit larger pupil diameter after light adaptation, as well as a reduced amplitude of contraction and a prolonged contraction time at light reflex, suggesting the existence of a pupillary imbalance mainly involving the parasympathetic system [45]. As for idiopathic RBD, one study showed a worse pupillomotor domain score of the composite autonomic scoring scale (COMPASS) in patients affected with the disorder compared with healthy controls [12]. However, pupillomotor function manifested on SCOPA-AUT was not different between idiopathic RBD patients and controls in the aforementioned multicenter case-controls study [14].

32.7 Pure Autonomic Failure and RBD

Pure autonomic failure (PAF) is a neurodegenerative disease that affects peripheral autonomic neurons with neuropathology almost identical to α-synucleinopathies. Patients affected with PAF typically present with symptomatic orthostatic hypotension and syncope, reduced sweating, erectile dysfunction, and constipation; a considerable number of patients have hyposmia and RBD. In a prospective cohort reported by Kaufmann et al. [46], 72% of PAF patients had probable RBD determined with clinical interviews and/or questionnaires at baseline [47, 48], and the presence of probable RBD was strongly associated with the development of manifest central nervous system (CNS) synucleinopathies within 4 years of follow-up. Interestingly, patients who phenoconverted to multiple system atrophy had severe bladder/bowel dysfunction and a cardiac chronotropic response upon tilt >10 beats per minute, while those who phenoconverted to PD or dementia with Lewy bodies had a lesser chronotropic response to tilt. This finding may suggest that both the presence of RBD and the severity of autonomic symptom in PAF patients are predictive of future phenoconversion to CNS synucleinopathies.

The first study of PSG confirmed RBD in PAF involved five patients who underwent extensive autonomic testing and met strict exclusionary criteria to be diagnosed with PAF and who also met video-PSG-confirmed diagnostic criteria for clinical RBD [49]. These five patients, and three other patients with PAF, had presented for video-PSG studies for various sleep complaints, including dream enactment. All patients demonstrated evidence of adrenergic failure on autonomic testing. The mean duration of autonomic symptoms was 11.2 years, and the mean duration of dream enactment was nearly 4 years. Therefore 5/8 PAF patients who had video-PSG studies met clinical and PSG diagnostic criteria for RBD. Therefore RBD in PAF may be more common than previously reported, and the presence of RBD suggests brain stem involvement in some cases of PAF.

32.8 Autonomic Dysfunction in Isolated REM Sleep Without Atonia (RWA)

In a study that reviewed 120 PSG records with RWA in patients without clinical RBD, after 99 records were discarded because of factors potentially affecting heart rate variability, the remaining 21 records were matched with 21 records of patients with normal REM atonia, and an electrocardiogram analysis was performed [50]. The parameters measured included R to R interval (RR) length, RR standard deviation, heart rate variability power, and very-low-frequency, low-frequency, and high-frequency bands.

Autonomic dysfunction was detected in a reduction in heart rate variability in the group with RWA compared to the group with normal REM atonia. Significant differences between the groups were demonstrated in RR standard deviation, heart rate variability power, and the low-frequency band. These findings confirmed the authors' hypothesis that heart rate variability would be reduced in patients with isolated RWA, and the abnormal findings were consistent with previous autonomic findings in clinic RBD. This was the first report of autonomic dysfunction in isolated RWA and encourages further evaluation of its clinical significance and potential implications of this finding (e.g., potential marker of future clinical RBD and/or evolving synucleinopathy).

32.9 Very Recent Publications

Three recent reports have been published in regard to RBD and the ANS, including a review of this topic from the perspective of synuclein neurodegeneration [51]. A prospective study of dementia predictors in 134 PD patients found that at 3.6-year follow-up, 26% (n = 35) developed dementia—and notably, the strongest determinant for dementia development was the coexistence of RBD, orthostatic hypotension, and mild cognitive impairment at baseline [52]. In another prospective study on predictive markers for early conversion from iRBD to synucleinopathy neurodegeneration in 43 patients, at 5-year follow-up, 42% (n = 18) had converted to neurodegeneration—and the strongest predictor of conversion was the combination of autonomic dysfunction (assessed by the Scale for Outcomes in Parkinson's Disease-Autonomic Questionnaire) and abnormal dopamine transporter uptake (DAT-SPECT imaging), which the authors stated could form the basis for future disease-modifying trials [53].

Conclusion

Autonomic symptoms are relatively common in patients with idiopathic RBD. The degree of the symptoms seem to remain intermediate between controls and patients with PD or DLB, and positivity for autonomic symptoms (especially isolated one) is thought to have low predictive value for future development of α-synucleinopathies. However, identification of pathological change responsible for the appearance of autonomic symptoms would possibly contribute to the prediction of the development.

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Cardiac Scintigraphy in RBD

33

Masayuki Miyamoto, Tomoyuki Miyamoto, and Koichi Hirata

33.1 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM parasomnia characterized by dream-enacting behavior that may cause injury or sleep disruption and is associated with REM sleep without atonia [1]. Uchiyama et al. [2] reported a neuropathologically confirmed incidental Lewy body disease (LBD) in a patient with long-standing iRBD. Boeve et al. [3] reported clinicopathologic correlations in 172 RBD cases with or without a coexisting neurologic disorder; among the neurodegenerative disorders associated with RBD, 94% were synucleinopathies. Schenck et al. [4] reported that 81% of elderly men initially diagnosed with iRBD developed parkinsonism/dementia over a mean 14 years of follow-up. Iranzo et al. [5] reported that 82% of 44 participants from their elderly iRBD cohort had developed Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), or mild cognitive impairment over a median of 10.5 years of follow-up. These long-term prospective studies have shown that most

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elderly iRBD patients will eventually develop an alpha-synuclein neurodegenerative disorder, with the rate of emergence depending on the length of the follow-up period. iRBD may therefore be one of the earliest signs of and/or a long-term predictor for alpha-synuclein neurodegenerative disorders. Conversely, RBD is present in >90% of reported MSA cases, in ~75% of reported DLB cases, and up to 46% of reported PD patients. Thus, current evidence suggests a selective association between RBD and α-synucleinopathies, and iRBD represents a prodromal phase of PD and DLB [1]. Patients with iRBD have been shown to perform poorly in tests of color vision, olfactory function, and motor speed, which are thought to be early markers of PD [6]. Autonomic cardiac denervation is one of the non-motor symptoms of PD [7]. In iRBD, autonomic dysfunction is consistent with an evolving neurodegenerative disorder. Cardiovascular autonomic dysfunction is particularly common in iRBD.

In this chapter, we review and focus on the findings and utility of cardiac ^{123}I-meta-iodobenzylguanidine (MIBG) scintigraphy, which enables the quantification of postganglionic cardiac sympathetic innervation, in iRBD and Lewy body-related diseases.

33.2 Noradrenaline and ^{123}I-MIBG Kinetics in the Cardiac Sympathetic Nervous System

33.2.1 Noradrenaline Kinetics in the Heart

Autonomic control of the heart involves the sympathetic and parasympathetic nervous systems that play an important role in the regulation of myocardial contraction, heart rate, and myocardial metabolism. Efferent sympathetic nerves descend in the spinal cord, synapse with preganglionic fibers and paravertebral stellate ganglia, and innervate the right ventricle and anterior/lateral left ventricle. In the heart, sympathetic nerves follow coronary arteries in the subepicardium, penetrating the myocardium to regulate cardiac function [8].

Noradrenaline is a neurotransmitter released from sympathetic nerve endings. Noradrenaline synthesis begins with the synthesis of dopamine; tyrosine is converted to levodopa via tyrosine hydroxylase and converted to dopamine by DOPA decarboxylase. β-Hydroxylase further hydroxylates dopamine into noradrenaline. When sympathetic nerves are excited, noradrenaline is released to increase heart rate and cardiac contractility through β-1 adrenergic receptors. Only a fraction of the released noradrenaline binds to receptors, and most of the remainder (80–95%) undergoes active reuptake into nerve endings (uptake-1 mechanism) to be restored in vesicles. The remaining noradrenaline remains within the blood. If it undergoes reuptake or is not taken up by passive diffusion, it is catabolized by catechol-*O*-methyltransferase (COMT) outside nerve cells. If it undergoes reuptake, but is not repackaged in noradrenaline-storing vesicles, it is catabolized by monoamine oxidase (MAO) (Fig. 33.1).

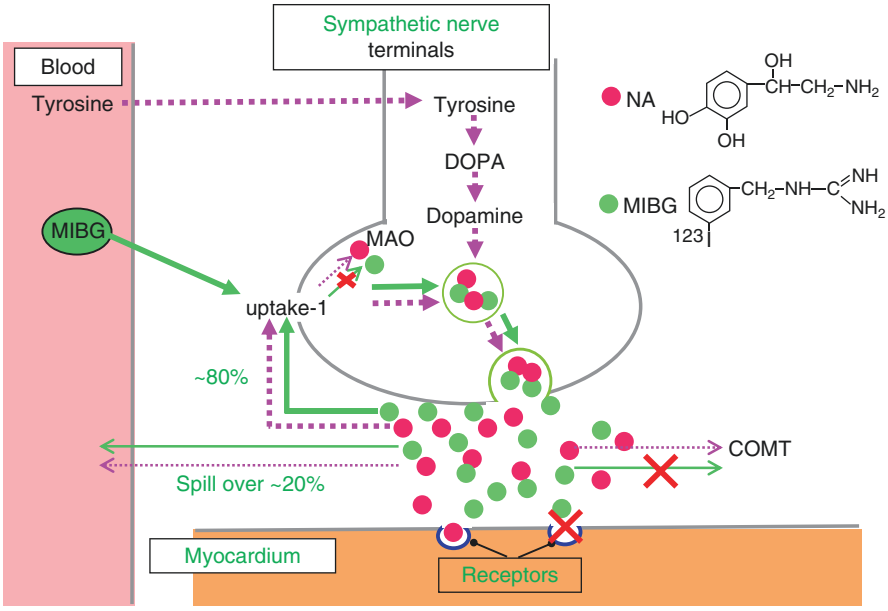

Fig. 33.1 Kinetics of noradrenaline and MIBG in cardiac sympathetic nerve endings. ^{123}I-MIBG, a guanethidine analog that is a radioactive tracer of noradrenaline, has an uptake (uptake-1 mechanism), storage, and release mechanism (exocytosis) similar to that of noradrenaline, but it is not catabolized by COMT or MAO. ^{123}I-MIBG does not bind to sympathetic receptors nor show physiological activity

33.2.2 ^{123}I-MIBG Kinetics in the Heart

MIBG, a guanethidine analog (an adrenergic neuron-blocking agent) that is a radioactive tracer of noradrenaline, has an uptake and storage mechanism similar to that of noradrenaline [9]. It is virtually the only radiotracer used for scintigraphy studies of the cardiac autonomic nervous system. The first cardiac imaging study in humans was conducted by Kline et al. [10]. MIBG is actively taken up into postganglionic presynaptic nerve endings in the adrenergic system by energy-dependent noradrenaline monoamine transporter 1 trapped in storage vesicles and is released by a mechanism similar to that of noradrenaline (exocytosis), but it is not catabolized by COMT or MAO [11]. Therefore, MIBG can determine the distribution, activity, and disorders of postsynaptic cardiac sympathetic nerves and is used widely to evaluate various kinds of heart disease, diabetes, and autonomic disorders, e.g., neurodegenerative disorders.

Reserpine markedly lowers the MIBG content of the adrenal medulla in dogs, but the adrenergic-blocking agents phenoxybenzamine and propranolol have no effect on MIBG uptake, indicating that MIBG does not bind to sympathetic receptors nor show physiological activity [12]. Therefore, MIBG imaging does not imply

a visualization of sympathetic receptors. A number of drugs are known to, or considered to, have an impact on MIBG uptake or storage [13]: inhibition of the sodium-dependent uptake system (uptake-1) from synaptic clefts (e.g., cocaine, tricyclic antidepressants, labetalol), inhibition of uptake by active transport into vesicles (e.g., reserpine, desmethylimipramine), competition for transport into vesicles (e.g., noradrenaline, serotonin, guanethidine), and depletion of storage vesicles (e.g., reserpine, labetalol, sympathomimetic drugs). Foods containing vanilla and catecholamine-like ingredients, e.g., chocolate and blue cheese, have high levels of tyramine, which acts as a catecholamine-releasing agent, and should be avoided approximately 6–12 h before MIBG imaging, to prevent any influence on MIBG uptake [14] (Fig. 33.1).

33.3 Technical Considerations for Cardiac ^{123}I-MIBG Scintigraphy

The most commonly used mean of imaging cardiac sympathetic denervation is cardiac ^{123}I-MIBG scintigraphy. A proposal for the standardization of cardiac ^{123}I-MIBG scintigraphy was published by the European Association of Nuclear Medicine [15].

In analyses of cardiac ^{123}I-MIBG scintigraphy, the most common measures are semiquantitative analyses of global uptake using the heart-to-mediastinum (*H*/*M*) ratio generated by planar imaging and differences in tracer uptake/retention in early and delayed images with the washout rate (WR). Semiquantitative cardiac ^{123}I-MIBG scintigraphy can be best performed using medium-energy collimators. Considerable data from ^{123}I-MIBG imaging have been generated from the analysis of planar images, mostly with a standard anterior view. Planar images of the thorax are acquired at ~15–30 min (early images) and 3–4 h (delayed images) after injection for 10 min. Single-photon emission computed tomography (SPECT) images can also be acquired using standard perfusion-imaging methods. Cardiac ^{123}I-MIBG uptake is determined semiquantitatively by calculating the *H*/*M* ratio after drawing regions of interest (ROIs) over the heart and upper mediastinum above the lung apices, but below the thyroid gland, in the planar anterior view. Average counts per pixel in the myocardium are divided by average counts per pixel in the mediastinum, thus generating the *H*/*M* ratio. Okuda et al. developed software to measure the *H*/*M* ratio semiautomatically (standardized method for automatic ROI setting in MIBG, smartMIBG) [16] (Fig. 33.2). The *H*/*M* ratios generated with this method were higher than those obtained manually, because the count point of the mediastinum ROI is minimal.

The early *H*/*M* ratio probably reflects receptor density, the integrity of presynaptic nerve terminals, and uptake-1 function. The delayed *H*/*M* ratio combines information on neuronal function from uptake to release through storage vesicles at nerve terminals and uptake-1 function. Cardiac ^{123}I-MIBG washout has been shown to be an important measure of cardiac sympathetic innervation; early and delayed planar images are used for this calculation.

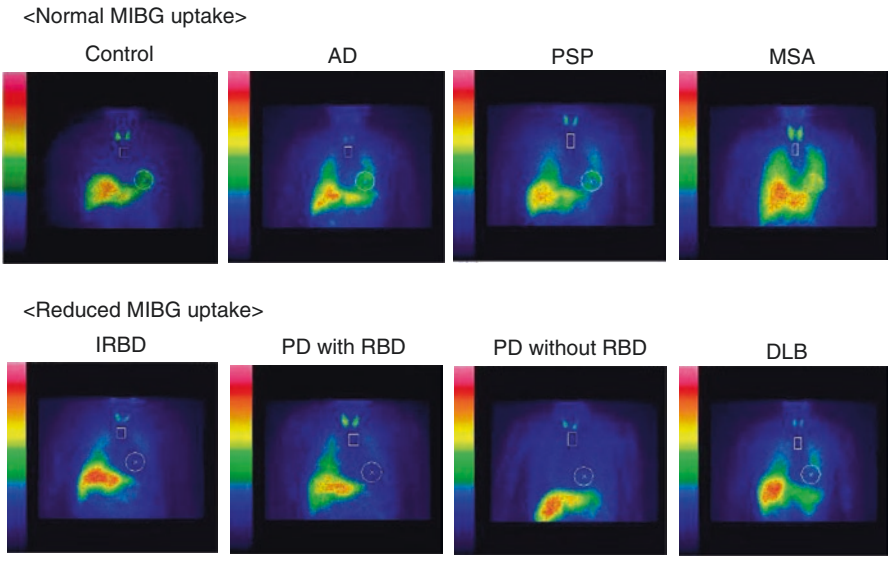

Fig. 33.2 Planar H/M ratio semiquantification of ^{123}I-MIBG uptake on the anterior view of the thorax. ^{123}I-MIBG H/M ratio in control, Alzheimer's disease (AD), progressive supranuclear palsy (PSP), multiple systemic atrophy (MSA), idiopathic REM sleep behavior disorders (iRBD), Parkinson's disease (PD), PD without RBD, and dementia with Lewy bodies (DLB). Regions of interest were positioned using smartMIBG software. Delayed *H*/*M* ratios were 2.67, 2.88, 2.59, 2.60, 1.12, 1.50, 1.07, and 1.51, respectively

The WR is thought to reflect catecholamine turnover, which is related to the degree of sympathetic drive. The WR is also calculated to evaluate sympathetic tone or drive as follows:

$$\mathrm{WR}(\%) = \left[\left(\left(H_{\mathrm{early}} - M_{\mathrm{early}}\right) - \left(H_{\mathrm{delay}} - M_{\mathrm{delay}}\right)\right) \times k\right] / \left(H_{\mathrm{early}} - M_{\mathrm{early}}\right) \times 100$$

where H_{early} and H_{delay} are the average heart counts and M_{early} and M_{delay} are the average mediastinal counts in early and delayed scans, respectively. The coefficient k is a time decay correction factor of $1/0.5^{t/13}$ for time t (hours) [17]. A normal WR value in control subjects is reported to be 10 ± 9%.

33.4 Pathological Background of Reduced Cardiac MIBG Uptake

Lewy bodies and neurites are found not only in the central nervous system but also in the peripheral autonomic nervous system, e.g., sympathetic ganglia, enteric nervous system of the alimentary tract, cardiac plexus, pelvic plexus, and adrenal medulla, in PD patients [18].

Degeneration of the cardiac sympathetic nerves occurs in PD and DLB. It begins during the early stages of PD, accounting for the reduced cardiac MIBG uptake, and

also in the early stages of LBD. Orimo et al. [19] demonstrated that degeneration of the distal axons of the cardiac sympathetic nerves precedes the loss of their mother neurons in the paravertebral sympathetic ganglia, suggesting the distal-dominant degeneration of the cardiac sympathetic nerves in PD. Postmortem studies have shown that tyrosine hydroxylase-immunoreactive axons in the heart are decreased, primarily due to degeneration of the cardiac sympathetic nerves in pathologically confirmed LBD, but not in other related disorders [20]. Thus, this supports the finding of reduced cardiac MIBG uptake in LBD.

Braak et al. [21] reported the detailed pathological stages for the progression of PD and suggested that early pathological changes in the central nervous system begin in the lower part of the brainstem (dorsal motor nucleus of the vagal nucleus) and olfactory bulb (anterior olfactory nucleus), even in the absence of nigral involvement. Orimo et al. [22] immunohistochemically examined the cardiac tissue, sympathetic ganglia, and medulla oblongata from patients with incidental LBD and suggested that degeneration of cardiac sympathetic nerves precedes neuronal cell loss and dysfunction in the dorsal vagal nucleus during the early stage of PD.

33.5 Findings of Cardiac ^{123}I-MIBG Scintigraphy in PD and Related Diseases

The first cardiac MIBG study in patients with neurodegenerative disorders, including PD, was reported by Hakusui et al. in 1994. Reduced cardiac ^{123}I-MIBG uptake was observed in patients with autonomic failure, mainly orthostatic hypotension, and in those without orthostatic hypotension [23]. Orimo et al. showed that the degree of cardiac ^{123}I-MIBG uptake correlates with that of cardiac sympathetic denervation in pathologically confirmed LBD; however, patients with PD and reduced cardiac ^{123}I-MIBG uptake showed normal left ventricular function on echocardiology [24], and the clinical symptoms of autonomic disorders associated with cardiac denervation are difficult to recognize. Reduced cardiac ^{123}I-MIBG uptake is associated with a reduced overshoot of phase IV on the Valsalva maneuver, indicating that reduced cardiac ^{123}I-MIBG uptake clinically reflects cardiac sympathetic dysfunction in PD patients [25]. Kim et al. [26] showed that RBD was closely associated with orthostatic hypotension and cardiac sympathetic denervation in patients with early and mild PD.

Reduced cardiac ^{123}I-MIBG uptake is not observed in MSA patients [27]. It may be difficult to differentiate PD clinically from other neurodegenerative diseases, e.g., MSA or progressive supranuclear palsy (PSP). Yoshita et al. investigated cardiac sympathetic function using cardiac ^{123}I-MIBG scintigraphy and found that the *H*/*M* ratio in planar imaging studies was significantly lower in PD patients compared with patients with MSA, PSP, or healthy controls [28]. In the early stages, cardiac ^{123}I-MIBG scintigraphy may help to differentiate PD from MSA or PSP. Braune et al. [27] showed that the *H*/*M* ratio was pathologically impaired in all patients with PD, independent of duration and the severity of autonomic and parkinsonian symptoms, and all patients with MSA had a normal *H*/*M* ratio. MIBG uptake showed a high sensitivity for the detection of autonomic involvement in PD patients and also a high specificity for the discrimination of PD and MSA.

These findings are supported by the observation that autonomic failure in PD is caused by damage of the postganglionic part of the autonomic nervous system, whereas in MSA, degeneration of preganglionic and central autonomic neurons is observed [27].

Orimo et al. [29] performed a meta-analysis of studies on the diagnostic performance of cardiac ^{123}I-MIBG scintigraphy for the differential diagnosis of PD and other neurodegenerative parkinsonism syndromes, especially MSA, PSP, and corticobasal degeneration. Thirteen studies comprising 625 PD patients and 220 with other neurodegenerative parkinsonism syndromes were analyzed. The pooled sensitivity and specificity to differentiate PD from other neurodegenerative parkinsonism syndromes of the early *H*/*M* ratio were 82.6% and 89.2%, respectively, and those of the delayed *H*/*M* ratio were 89.7% and 82.6%, respectively. When PD was limited to the early stage (Hoehn-Yahr 1 or 2), the pooled sensitivity and specificity of the delayed *H*/*M* ratio were 94.1% and 80.2%, respectively.

33.6 Findings of Cardiac ^{123}I-MIBG Scintigraphy in DLB and Other Forms of Neurodegenerative Dementia

DLB patients generally show markedly reduced cardiac ^{123}I-MIBG uptake, regardless of the presence of parkinsonism [30, 31]. The antemortem diagnosis of DLB needs to be distinguished from Alzheimer's disease (AD) because of important differences in patient management and outcome. Yoshita et al. [30] showed a clinically important discrimination between DLB and AD: the delayed *H*/*M* ratio had a sensitivity of 100%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 100% at a cutoff value of 1.68. Hanyu et al. [32] reported that cardiac ^{123}I-MIBG scintigraphy (reduction in cardiac ^{123}I-MIBG uptake) might be a powerful differential diagnostic tool when it is difficult to distinguish DLB from AD using brain perfusion SPECT (medial occipital hypoperfusion).

In a multicenter study, using the *H*/*M* ratio calculated with the automated system, when applying a cutoff value of 2.10 for both early and delayed *H*/*M* ratios, the sensitivity was 68.9%, and specificity was 89.1% to differentiate probable DLB from probable AD in both early and delayed images. In a subpopulation of patients with mild dementia (MMSE $\geq$ 22), the sensitivity and specificity were 77.4% and 93.8%, respectively, when applying a cutoff value of 2.10 to the delayed *H*/*M* ratio. This diagnostic accuracy is sufficiently high to be clinically useful to distinguish DLB from AD, especially in patients with mild dementia [31].

33.7 Findings of Cardiac ^{123}I-MIBG Scintigraphy in Idiopathic RBD

33.7.1 Cross-sectional Studies

iRBD likely represents a prodromal stage of α-synucleinopathies.

Miyamoto et al. [33] reported markedly reduced cardiac ^{123}I-MIBG uptake, consistent with the loss of sympathetic terminals, in iRBD. Their study included 13

iRBD patients, 12 PD patients, and 8 control subjects. Mean ^{123}I-MIBG uptake in the delayed *H*/*M* ratio was significantly reduced in patients with iRBD (1.34 ± 0.20) or PD (1.43 ± 0.20) compared to controls (3.01 ± 0.39) (each $p < 0.001$). All of these iRBD patients displayed a reduction in cardiac ^{123}I-MIBG uptake, and uptake was also markedly reduced in the PD patients; this reduction in the iRBD patients was of the same magnitude as that in the PD patients [33] (Table 33.1). These results are consistent with the hypothesis that iRBD in older patients is a forme fruste of LBD, including PD and DLB. Miyamoto et al. [34] compared the tracer uptake of cardiac ^{123}I-MIBG among iRBD ($n = 31$), PD ($n = 26$), MSA ($n = 10$), DLB ($n = 6$), PSP ($n = 13$), and control subjects ($n = 9$). The mean *H*/*M* ratio (early, delayed) was significantly reduced in patients with iRBD compared to MSA, PSP, and control subjects ($p < 0.001$ in each group). Cardiac ^{123}I-MIBG findings were similar among iRBD and LBD (PD and DLB) patients, but different from those of PSP and MSA patients. A marked reduction in cardiac ^{123}I-MIBG uptake was found in patients with iRBD compared to control subjects and patients with clinically diagnosed PD and DLB (Table 33.1). These findings that the degree of reduction in cardiac ^{123}I-MIBG uptake was similar in patients with iRBD compared with PD and DLB patients support the notion that Lewy body-related α-synucleinopathies, including PD, DLB, and pure autonomic failure, represent a clinical and pathologic spectrum.

Kashihara et al. [35] reported a case of iRBD who showed reduced cardiac ^{123}I-MIBG uptake and then studied 13 iRBD patients, 222 PD patients, and 50 controls [36] (Table 33.1). *H*/*M* ratios were lower in the PD patients and decreased with disease progression. However, they showed that cardiac ^{123}I-MIBG uptake was more markedly reduced in patients with iRBD than in those with early stage PD (Hoehn-Yahr 1 and 2). Their findings suggest that the lesion responsible for the reduction of ^{123}I-MIBG uptake is located or linked more closely to RBD development compared to PD development. As far as these cardiac ^{123}I-MIBG uptake results are concerned, the authors suggested that iRBD may not necessarily be a prodromal condition of PD with respect to cardiac ^{123}I-MIBG uptake results.

Interestingly, Miyamoto et al. [37] compared cardiac ^{123}I-MIBG uptake in patients with polysomnography-confirmed iRBD with that in patients with PD with clinically probable RBD (pRBD), patients with PD without pRBD, and control subjects. The H/M ratios for iRBD and PD with or without pRBD were significantly reduced in both the early and delayed images as compared with the control values. The *H*/*M* ratio for PD with pRBD was significantly reduced in both early and delayed images compared with the values for PD without pRBD ($p < 0.05$, $p < 0.01$, respectively), but did not differ significantly between patients with iRBD and PD with pRBD (Table 33.1).

Koyama et al. [38] reported on a 66-year-old iRBD patient with hyposmia and impaired facial expression recognition (that may reflect dysfunction of the amygdala) and reduced cardiac ^{123}I-MIBG uptake (Table 33.1). In RBD, therefore, neurodegeneration may occur more diffusely than in the brainstem alone.

Oguri et al. [39] presented two RBD patients with different clinical progression (Table 33.1). One 69-year-old patient with a >20-year history of iRBD showed

Table 33.1 Findings of cardiac ^{123}I-MIBG scintigraphy in idiopathic RBD, neurodegenerative diseases, and obstructive sleep apnea

Author	Year		*n*	Age, years	Disease duration, years	Early *H/M* ratio	Delayed *H/M* ratio
Miyamoto T	2006 [33]	iRBD	13	68.4 ± 7.5	5.5 ± 3.7		1.34 ± 0.20
		PD	12	68.4 ± 5.3			1.43 ± 0.20
		Control	8	71.9 ± 8.2			3.01 ± 0.39
Kashihara	2007 [35]	iRBD	1	60	3	1.3	1.06
Kohyama	2007 [38]	iRBD	1	60	1.5	1.87	1.39
Miyamoto T	2008 [34]	iRBD	31	66.3 ± 6.7	5.7 ± 4.9	1.70 ± 0.39	1.49 ± 0.39
		PD	26	67.5 ± 6.3	1.9 ± 1.3	2.08 ± 0.55	1.80 ± 0.68
		DLB	6	71.0 ± 5.9	0.9 ± 0.2	1.52 ± 0.13	1.29 ± 0.12
		MSA	10	64.7 ± 9.0	2.5 ± 1.5	2.57 ± 0.49	2.91 ± 0.53
		PSP	13	70.7 ± 7.6	2.3 ± 1.4	2.86 ± 0.34	3.03 ± 0.41
		Control	9	72.2 ± 7.7		2.81 ± 0.37	3.06 ± 0.39
Oguri	2008 [39]	iRBD	2				
		Patient 1		69	20	1.29	1.12
		Patient 2		66	7	1.5	1.3
				69[a]		1.48	1.3
Miyamoto T	2008 [45]	iRBD	47				
		AHI < 5/h	23	65.2 ± 6.5		1.63 ± 0.21	1.34 ± 0.19
		5 ≤ AHI < 15/h	9	66.0 ± 5.2		2.01 ± 0.63	1.67 ± 0.62
		AHI ≥ 15/h	15	67.1 ± 8.1		1.66 ± 0.28	1.36 ± 0.27
		OSA, AHI ≥ 15/h	16	59.8 ± 10.6		2.66 ± 0.39	2.82 ± 0.56
		OSA with DEB	5			2.73 ± 0.50	3.03 ± 0.66
Miyamoto T	2010 [40]	iRBD	1	71	4	1.68	1.45
				73		1.36	1.12

(continued)

Table 33.1 (continued)

Author	Year		*n*	Age, years	Disease duration, years	Early *H/M* ratio	Delayed *H/M* ratio
Miyamoto T	2010 [43]	iRBD	15	67.5 ± 6.3	3.2 ± 7.9		1.53 ± 0.36
				Follow-up duration	2.51 ± 0.81		1.45 ± 0.25
		PD	11	66.6 ± 7.5	4.1 ± 3.1		1.77 ± 0.64
				Follow-up duration	3.19 ± 1.87		1.58 ± 0.40
Kashihara	2010 [36]	iRBD	13	71.8 ± 6.4	2.8 ± 3.1	1.57 ± 0.37	1.39 ± 0.40
		PD	222	73.0 ± 8.6	5.4 ± 5.4	1.74 ± 0.38	1.55 ± 0.45
		Control	50	73.8 ± 8.9		2.36 ± 0.26	2.57 ± 0.35
Miyamoto T	2011 [37]	iRBD	59	66.9 ± 5.4	6.5 ± 9.7	1.79 ± 0.30	1.42 ± 0.26
		PD with cpRBD	11	66.2 ± 5.7	5.9 ± 5.9	1.87 ± 0.31	1.48 ± 0.22
		PD w/o cpRBD	27	67.9 ± 6.4	4.3 ± 4.3	2.25 ± 0.55	1.98 ± 0.65
		Control	19	61.9 ± 6.7		2.78 ± 0.30	2.87 ± 0.45
Miyamoto T	2017[b]	iRBD	25[b]	66.7 ± 7.3[b]		1.72 ± 0.23[b]	1.36 ± 0.20[b]

H/M ratio heart-to-mediastinum ratio, *iRBD* idiopathic REM sleep behavior disorder, *PD* Parkinson's disease, *DLB* dementia with Lewy bodies, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy, *OSA* obstructive sleep apnea, *AHI* apnea hypopnea index, *DEB* dream-enacting behavior, *PD with cpRBD* PD with clinical probable RBD, *PD w/o cpRBD* PD without clinical probable RBD

[a]Developed mild parkinsonism at age 68

[b]*H/M* ratio was standardized for various collimators (unpublished data)

reduced cardiac ^{123}I-MIBG uptake in early and delayed *H*/*M* ratios of 1.29 and 1.12, respectively. The other 69-year-old patient started to manifest abnormal nocturnal behavior at the age of 62, mild parkinsonism at age 68, and reduced cardiac ^{123}I-MIBG uptake before and after the onset of parkinsonism. In the first study, an early *H*/*M* ratio of 1.50 and delayed *H*/*M* ratio of 1.30 were observed, while the second study detected an early *H*/*M* ratio of 1.48 and delayed *H*/*M* ratio of 1.30. They showed that iRBD could develop in diverse patterns of clinical progression, even if there are underlying signs of Lewy body pathology.

33.7.2 Follow-Up Studies

Miyamoto et al. [40] followed a 73-year-old man with iRBD by CFI-PET immediately after the development of iRBD and yearly for 2.5 years. Nigrostriatal presynaptic dopaminergic function was normal at 1 year after diagnosis and decreased by 4–6% per year, which is similar to that found in PD, but reduced cardiac ^{123}I-MIBG uptake and orthostatic hypotension had already appeared at the onset of iRBD, indicating that the degeneration of non-motor neurons preceded that of motor neurons.

Paglionico et al. [41] described a 72-year-old woman with iRBD and a marked decrease of cardiac ^{123}I-MIBG uptake but intact striatal dopaminergic neurons. The imaging studies of Salsone et al. indicated that cardiac sympathetic denervation precedes nigrostriatal damage in iRBD [42].

Miyamoto et al. [43] reported cardiac ^{123}I-MIBG scintigraphy findings in patients with iRBD and PD. After the initial ^{123}I-MIBG scintigraphy, the subjects were retested after a mean of 2.8 years. The delayed *H*/*M* ratio was not significantly reduced between the first and second study in either group. Follow-up imaging revealed a mean decline of 4.21 ± 9.06% or 6.40 ± 19.02% in the delayed *H*/*M* ratio in those with iRBD or PD, respectively (Table 33.1). These cardiac ^{123}I-MIBG uptake findings might indicate progression early in the course of iRBD or PD, but this progression is heterogeneous and independent of the development of motor symptoms.

33.8 Utility of Cardiac ^{123}I-MIBG Scintigraphy to Differentiate Idiopathic RBD and "Pseudo" RBD

Dream enactment behavior is a core feature of RBD, but similar behavior can also occur in untreated obstructive sleep apnea syndrome (OSAS). The REM sleep fragmentation of OSAS (obstructive respiratory events) can lead to dream enactment behavior, but this typically resolves with continuous positive airway pressure therapy that fully controls the OSAS. There has been one carefully documented case series of OSAS simulating the clinical features of RBD with dream enactment, which is called OSAS "pseudo" RBD [44]. The usefulness of video-polysomnography to differentiate between confusional arousals from sleep with dream enactment occurring at the resumption of breathing after apnea in OSAS and dream-related

behaviors in RBD patients has been reported. However, dream-related behavior may not always occur in laboratory sleep studies.

Miyamoto et al. [45] investigated cardiac ^{123}I-MIBG scintigraphy as a supportive diagnostic indicator for iRBD complicated with moderate-to-severe OSAS. Cardiac ^{123}I-MIBG uptake based on the *H*/*M* ratio was significantly decreased in iRBD patients with or without OSAS compared with patients with moderate-to-severe OSAS without RBD (Table 33.1). Receiver operator characteristic analyses revealed that a cutoff value of 1.97 for the delayed *H*/*M* ratio was useful for differentiating iRBD complicated by moderate-to-severe OSAS from moderate-to-severe OSAS without RBD. Thus, cardiac ^{123}I-MIBG scintigraphy has the potential to distinguish true RBD from pseudo RBD associated with OSAS.

33.9 Conclusion and Future Directions

RBD is a heterogeneous disease. Reduced cardiac ^{123}I-MIBG uptake is a potential diagnostic marker of RBD with Lewy body-related pathology. We believe that cardiac ^{123}I-MIBG scintigraphy may be a very useful diagnostic tool for RBD with Lewy body-related syndrome. Neuropathological studies will be required to support this hypothesis.

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Neuropsychological Aspects: Cognition in RBD

34

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34.1 Introduction

It is well recognized that idiopathic rapid eye movement sleep behavior disorder (iRBD) is a major risk factor for synucleinopathies, a category of neurodegenerative diseases that includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Several risk factors and biomarkers of synucleinopathies have been identified in iRBD. Cognitive markers are particularly useful for describing iRBD subtypes (with or without mild cognitive impairment [MCI]) and to predict whether RBD patients will develop dementia first (DLB) or parkinsonism first (MSA or PD). Individuals with PD and concomitant RBD present a different clinical phenotype, with more impaired brain functional and anatomical substrates and a higher risk of presenting MCI and developing dementia.

34.2 Idiopathic RBD and Dementia Risk

DLB is the second most common cause of degenerative dementia in people older than 65 years [1]. Compared to Alzheimer's disease, DLB is associated with accelerated cognitive decline, shorter lifespan, less favorable prognosis, increased admission to residential care, and higher caregiver burden and health-related costs [1]. DLB is defined as a progressive cognitive decline with altered usual daily activities accompanied by a set of core clinical features, namely, (1) fluctuating cognition with pronounced variations in attention and alertness; (2) recurrent visual hallucinations; (3) RBD, which may precede cognitive decline; and (4) one or more

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spontaneous cardinal features of parkinsonism (bradykinesia, rest tremor, or rigidity) [2]. DLB is similar to PD with dementia (PDD), suggesting a common spectrum of Lewy body disease [2]. However, mainly for clinical purposes but also for research, a distinction between these two clinical entities has been proposed based on the temporal sequence of symptom appearance: PDD should be diagnosed when dementia occurs 1 year after a well-established PD diagnosis, whereas DLB should be diagnosed when dementia occurs before or at the same time as parkinsonism [2]. The cognitive profile of DLB patients typically involves severely impaired visuospatial abilities, attention capacities, executive functions, and, to a lesser extent, learning and memory functions [1].

Longitudinal studies in iRBD cohorts at a sleep center found an almost equivalent risk of developing parkinsonism first (PD or MSA) or dementia first (DLB). Schenck et al. [3] followed 26 patients for a mean of 14.2 years after RBD onset. Of the 21 patients who developed a neurodegenerative disease, 6 (29%) were diagnosed with dementia (3 DLB, 1 unspecified, and 2 Alzheimer's disease with autopsy-confirmed combined Alzheimer's plus Lewy body disease pathology). Another study followed 174 iRBD patients for a mean of 12 years after RBD onset [4]. Of the 53 patients who developed a synucleinopathy, 29 (55%) were diagnosed with DLB. Recently, our group published the results on a cohort of 89 iRBD patients followed for a mean of 14.6 years after RBD symptom onset. Of the 46 patients diagnosed with a synucleinopathy, 21 (46%) developed DLB [5]. Finally, Youn et al. [6] followed 84 patients for a mean of 8.2 years after RBD onset. Of the 18 patients who developed a neurodegenerative disease, 7 (39%) had dementia (4 DLB, 3 Alzheimer's disease). Thus, the risk of developing dementia (mostly DLB) in iRBD is from 29 to 55% over a period of 8–14 years following RBD symptom onset. In contrast, only a few cases of iRBD developed Alzheimer's disease, and the association between RBD and Alzheimer's disease could be considered rare [7–9]. Taken together, these previous results support that RBD patients who develop dementia would present DLB at clinical diagnosis. Moreover, the inclusion of RBD as a core clinical feature improves the diagnostic accuracy of DLB [10], and RBD is now recognized as a core clinical feature of DLB [2].

34.3 Cognitive Profile in iRBD

34.3.1 Cross-sectional Studies

Of the many cognitive domains that have been defined, a neuropsychological assessment would consider in general mainly attention, executive functions, episodic learning and memory, visuospatial abilities, language, gnosia, and praxis. Cognitive complaints are frequent in iRBD patients [11], and several studies have found lower cognitive performance in iRBD patients compared to age-, sex-, and education-equivalent healthy subjects (Table 34.1) [6, 11–19]. All studies found lower performance by iRBD patients compared to healthy subjects on a broad range of cognitive tasks used in clinical settings. However, results vary across studies according to the cognitive domains that are impaired or preserved. Several factors may explain these discrepancies, including

Table 34.1 Controlled studies on cognitive performance in idiopathic rapid eye movement sleep behavior disorder

Variable	Terzaghi et al.	Massicotte-Marquez et al.[a]	Gagnon et al.[a]	Marques et al.	Ferini-Strambi et al.[b]	Fantini et al.[b]	Li et al.	Youn et al.	Zhang et al.	Barder et al.
Number of patients	23	14	32	10	17	24	23	96	15	171
Age	67.0 ± 7.0	66.6 ± 7.7	65.7 ± 8.5	64.0 ± 2.9	70.0 ± 7.3	69.5 ± 7.3	72.5 ± 6.8	65.5 ± 6.7	61.7 ± 12.7	64.7 ± 9.0
Education	6.0 ± 2.0	12.2 ± 4.0	13.4 ± 3.6	10.0 ± 0.6	8.5 ± 3.4	8.6 ± 3.6	14.2 ± 2.3	12.7 ± 4.9	10.4 ± 3.7	13.7 ± 3.4
Gender, % men	91	100	78	80	76	75	83	69	73	88
Cognitive domains										
Attention	Yes	No	Yes	No	Yes	No	No	Yes	No	–
Executive functions	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Verbal learning	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	–
Nonverbal learning	Yes	–	–	–	Yes	Yes	Yes	No	No	–
Visuospatial	No	No	No	–	Yes	Yes	Yes	Yes	No	–
Language	–	–	–	–	–	–	No	–	No	–
Gnosia	–	–	–	–	–	–	–	–	–	–
Praxis	–	–	–	–	–	–	–	–	–	–

[a,b]share common participants; Yes = poorer performance for patients versus controls ($p < 0.05$); No = similar performance for patients and controls

population heterogeneity in the sociodemographic variables, recruitment bias, small sample sizes with low statistical power, and the use of diverse cognitive tasks with variable specificity to a cognitive domain and variable sensitivity to detect deficits.

Generally, the most affected cognitive domains in iRBD are attention, executive functions, and episodic memory [11–19]. Additionally, some studies have found impaired visuospatial abilities [6, 12–14], although others have not [11, 16–18]. In fact, impaired visuospatial, visuoperceptive, and nonverbal learning abilities in iRBD appear to be related to the extent of cognitive decline [12, 20–22], as has been reported for neurodegenerative diseases associated with RBD, such as PD and DLB [11, 23]. Moreover, the use of more sensitive computerized tasks might reveal visuoperceptive and visual short-term memory deficits in iRBD [15, 24, 25]. Praxis, gnosia, and language appear to be well preserved in iRBD, although these cognitive functions, or their more specific components, have received little research attention. Overall, the impaired cognitive profile observed in iRBD is similar, albeit to a lesser extent, to that observed in DLB.

Recent iRBD studies have examined other cognitive functions, including prospective memory and decision-making [[26, 27]; see Chap. 35]. Prospective memory refers to the ability to execute delayed intentions, such as remembering to attach an important document to an email or to take a pill at bedtime [28]. Significant prospective memory decline has been reported in PD patients [29, 30]. In a recent study by our group, prospective memory was assessed in iRBD using a self-administered questionnaire, a simple clinical measure (envelope test), and a laboratory general knowledge task involving perceptual cue salience [31]. All participants performed well on the questionnaires and the envelope task. However, healthy subjects showed better detection accuracy compared to iRBD patients for all high- and low-salience cues. Moreover, iRBD patients with cognitive impairment performed similarly to iRBD patients with normal cognition in the high-salience condition but showed significant difficulty in detecting low-salience cues. Thus, prospective memory difficulties in iRBD, assessed with a laboratory task, are more prominent in patients with cognitive impairment and could serve as a promising indicator of early cognitive decline in iRBD. One recent study also found evidence for a differential pattern of prospective memory impairment in iRBD with severe impairment of event-based and concurrent preservation of time-based prospective memory [32].

Most studies have focused on group differences in neuropsychological tests between healthy subjects and iRBD patients. However, the most relevant clinical variable is the proportion of iRBD patients with clinically significant cognitive impairment. A few studies have reported that a significant proportion of iRBD patients present clinically impaired cognition, particularly in terms of attention, executive functions, and episodic learning and memory [11, 16].

34.3.2 Longitudinal Studies

To our knowledge, five longitudinal studies have addressed cognition in iRBD. In the first study, 24 iRBD patients and 12 healthy subjects were followed for a mean

interval of 2.2 years [12]. Patients showed poorer delayed verbal memory (story recall) and visuospatial abilities (Rey-Osterrieth Complex Figure, copy) at baseline and follow-up and poorer visuospatial attention (Corsi supraspan test) at follow-up only. The second study followed 20 iRBD patients for a mean interval of 3.6 years [33]. Cognitive performance declined in 45% of patients, mainly in visuospatial abilities, along with nonverbal logic (Raven Coloured Matrices) and attention (Attentive matrices). The third study followed 84 iRBD patients for a mean of 4.2 years [6]. At follow-up, 18 patients had developed a neurodegenerative disease, including 7 with dementia. Only poorer visual attention (Trail Making Test, part A) at baseline differentiated between disease-free patients and those who developed a neurodegenerative disease. The fourth study followed 76 iRBD patients for a mean of 3.6 years [20]. At follow-up, 34 patients had developed a synucleinopathy: 15 dementia first (DLB) and 19 parkinsonism first (PD or MSA). Cognitive performance and the proportion of patients with clinically impaired performance (z score of -1.5) were compared at baseline between patients who developed dementia first and those who developed parkinsonism first. The diagnostic value of cognitive tests for detecting prodromal dementia was also assessed. RBD patients who developed dementia first were impaired at baseline in all cognitive domains (attention and executive functions, episodic learning, and visuospatial abilities) compared to patients who developed parkinsonism first. The parkinsonism-first patients were similar at baseline to disease-free iRBD patients on all cognitive measures. In dementia-first patients, two cognitive tests assessing attention and executive functions (Stroop Color-Word Test and Trail Making Test part B) best predicted dementia (area under the curve ≥ 0.85) compared to parkinsonism-first patients and healthy individuals.

In the more recent fifth study, we compared the progression of cognitive test performance over a six-year prodromal period in three groups of RBD patients classified at their last follow-up as having PD, DLB, or still-idiopathic [34]. Cognitive performance changes over time were strongly associated with later development of dementia (DLB). Clear deficits in attention and executive functions were observed 6 years before diagnosis. Verbal episodic learning and memory deficits started later, deviating from normal approximately 5 to 6 years and becoming clinically impaired 2 years before diagnosis. Visuospatial abilities progressed variably, with inconsistent prodromal latencies. For clinical utility, the Trail Making Test (part B) best detects early prodromal DLB stages, whereas Verbal Fluency (semantic) and Rey Auditory-Verbal Learning Test are best for monitoring changes over time.

34.4 MCI in iRBD

MCI is a syndrome known to be an intermediate state between normal cognitive functioning and dementia [35]. It is characterized by a significant, objectively assessed cognitive decline that is greater than expected for education and age. No major interference with social, professional, or daily living activities should be reported. MCI can be diagnosed according to the following criteria: (1) cognitive concern reflecting a significant change in cognition reported by the patient or a

relative or a health professional, (2) objective evidence of impairment in one or more cognitive domains compared with normative age- and education-equivalent performance, (3) preserved daily life activities based on previous and actual capacities, and (4) absence of dementia [11, 35]. In addition, medication side effects and other medical (e.g., severe sleep apnea, chronic obstructive pulmonary disease) or psychiatric conditions responsible for cognitive deficits should be excluded. MCI can be classified into different subtypes according to the nature (amnestic vs. non-amnestic) and number (single-domain vs. multiple-domain) of the cognitive domains impaired [36]. MCI is a risk factor for dementia, and depending on the etiology, many MCI patients develop AD, vascular dementia, PDD, or DLB [20, 37, 38]. However, the progression of MCI is also highly variable. In the general population and in PD patients, some MCI patients progress to dementia, others return to normal cognitive functioning, and still others remain with mild cognitive deficits for many years [38–40]. Consequently, clinicians and researchers should be careful not to directly link MCI to the future development of a neurodegenerative disease, nor to automatically consider MCI as part of a neurodegenerative disease.

In a population-based sample followed prospectively for a median of 3.8 years, a substantial proportion (14/44, or 32%) of individuals with probable RBD developed MCI [41]. Sleep clinic studies have also reported a high frequency of MCI in iRBD patients [4, 5]. In a cross-sectional study of iRBD patients referred to a sleep clinic, MCI frequency as measured by standard criteria was estimated at up to 50% (16/32) compared to 8% (3/40) in healthy subjects [11]. In this study, the main MCI subtype reported was nonamnestic MCI single domain with predominant attention and executive dysfunctions. Another study confirmed these results and found a higher proportion of MCI in iRBD patients (33%, 5/15) than in healthy subjects (8%, 3/36) [18]. Very few studies have followed a cohort of iRBD patients with concomitant MCI to determine the risk of developing dementia. Molano et al. [22] followed seven iRBD patients for several years. All patients met MCI criteria and subsequently developed Lewy body disease, confirmed by autopsy [22]. In a more recent study by our group, a large cohort of iRBD patients was followed for a mean of 3.6 years to determine the predictive value of MCI for dementia [20]. Results showed that a higher proportion of patients who developed dementia first had MCI at baseline (93%, or 14/15) compared to the proportion of patients that developed parkinsonism first (42%, or 8/19).

A comprehensive neuropsychological assessment is the most effective way to detect MCI. However, this involves a time-consuming exam that requires specialized training, which is often unavailable in clinical sleep practice. Effective MCI screening tests in iRBD would therefore be useful. Three screening tests have been tested in small cohorts for their ability to detect MCI in iRBD [42–44]: the Montreal Cognitive Assessment or MoCA [45], the Mini-Mental State Examination [46], and the Mattis Dementia Rating Scale [47]. The Mattis Dementia Rating Scale (cutoff score <141/144 indicating MCI) and MoCA (cutoff score <26/30 indicating MCI) show superior psychometric properties to the Mini-Mental State Examination. Nevertheless, due to its short administration time (5–10 min), its validated alternative versions (allowing retesting), the fact that it is available free of charge, and the fact that it does not require specialized training, the MoCA (http://www.mocatest.org/)

appears to be the most appropriate screening test for detecting MCI in iRBD. However, results should be validated in larger cohorts and in other countries with different cultures and languages.

The presence of cognitive impairment in a subgroup of iRBD patients suggests distinct clinical phenotypes and patterns of neurodegeneration. Only a few studies have investigated whether RBD patients show different cerebral functioning according to their cognitive status. Using quantitative EEG, Iranzo et al. [48] followed for a mean of 2.4 years 23 iRBD patients, including 10 who developed MCI, 13 who remained cognitively normal, and 10 healthy subjects. They recorded baseline EEG activity during wakefulness in the central and occipital areas and found higher absolute theta and delta power in iRBD patients who later developed MCI compared with healthy subjects, but no significant differences between the two RBD groups. Sasai et al. [49] examined 31 iRBD patients and found as their main results relationships among lower scores on the MoCA, olfactory dysfunction, and higher EEG delta spectral power during REM sleep in the occipital region. Rodrigues Brazète et al. [50] compared waking EEG activity in 42 iRBD patients, including 23 with MCI and 19 without MCI, and in 37 healthy subjects. iRBD patients with MCI had a higher slow-to-fast frequency ratio than iRBD patients without MCI and healthy subjects, mainly in the posterior regions (parietal, temporal, and occipital). iRBD patients without MCI were similar to healthy subjects.

Vendette et al. [51] investigated 20 patients with iRBD, including 10 with MCI and 10 without MCI, and 20 healthy subjects, using single-photon emission computed tomography (^{99mc}Tc-ethylene cysteinate dimer). Compared to healthy subjects, both iRBD groups had hypoperfusion in the frontal lobes. In addition, iRBD patients with MCI showed additional hypoperfusion in temporal, parietal, and occipital areas compared to RBD patients without MCI and healthy subjects. Taken together, these results indicate a more altered pattern of functional cerebral activity in iRBD patients with concomitant MCI, with hypoperfusion, and with EEG slowing, mainly in posterior regions. This functional activity pattern resembles that found in iRBD patients at risk for neurodegenerative disease, in DLB patients, and in PD patients at risk for dementia [52–58], providing new potential markers for increased risk of developing DLB in RBD patients with MCI. A recent study also found an association between cognitive dysfunction and pareidolias in iRBD patients [59]. Pareidolias are complex visual illusions of meaningful objects deriving from ambiguous forms embedded in visual scenes and a potential surrogate indicator of visual hallucinations, a core clinical feature of DLB [2].

The pathophysiology of MCI and cognitive impairment in iRBD remains poorly understood. Some studies have reported neuroanatomical and neurochemical deficits in iRBD. Indeed, white matter integrity loss and lower gray matter volume and thinning in cortical and subcortical regions are well documented in iRBD patients [60–65]. Neural loss has also been reported in several cortical and subcortical structures in iRBD [7, 66, 67]. In addition, nigrostriatal and nigrocaudate dopaminergic deafferentation have been reported in iRBD [68–70], while the serotoninergic systems remain intact [69]. Cholinergic and noradrenergic systems have been understudied in iRBD. One study used transcranial magnetic stimulation (short latency

afferent inhibition) and suggested cholinergic dysfunction in some iRBD patients who developed cognitive impairment [71]. However, none of these studies looked for the presence of MCI or cognitive impairment in their RBD population. In a recent study, we investigated cortical and subcortical gray matter abnormalities underlying cognitive deficits in iRBD patients with (n=17) or without (n=35) MCI and 41 healthy subjects [72]. Patients with MCI had cortical thinning in the frontal, cingulate, temporal, and occipital cortices, and abnormal surface contraction in the lenticular nucleus and thalamus. Patients without MCI had cortical thinning restricted to the frontal cortex. Lower performance in cognitive domains was associated with cortical and subcortical abnormalities in iRBD patients. In PD, the presence of a dysexecutive syndrome seems to be associated with dopaminergic dysfunction, whereas the development of dementia would be related to cholinergic degeneration [73, 74]. Interestingly, cholinergic dysfunction has also been related to RBD in PD [75]. Based on the strong associations between PD, RBD, and cognitive impairment, we may hypothesize that both dopaminergic and cholinergic deficiencies could be related to cognitive impairment in iRBD.

34.5 Cognitive Decline in PD Associated with RBD

A substantial proportion of PD patients have cognitive impairment, and approximately 75% will develop dementia during the course of PD [76]. RBD is also a frequent feature of PD, affecting 33–46% of patients [77, 78]. The existence of a distinct and more impaired cognitive profile in nondemented PD patients based on the presence of RBD is controversial [79]. Indeed, some studies have found in PD with RBD poorer cognitive performance and higher MCI frequency than in PD without RBD and healthy subjects [11, 15, 18, 80–86], whereas others have not [87–93]. However, most of these studies have methodological limitations that could explain the divergent results, including small sample size, use of screening tests only with poor sensitivity to measure cognition and that do not allow MCI diagnosis, absence of a healthy subject group to better interpret the results, and absence of polysomnography to diagnose RBD. Our group recently examined with a complete neuropsychological assessment 162 participants, including 53 PD patients with RBD confirmed by polysomnography, 40 PD patients without RBD, and 69 healthy subjects [94]. PD patients with RBD had poorer and clinically impaired (z score of -1.5) performance on several cognitive tests and domains compared to PD patients without RBD and healthy subjects, who performed similarly on all cognitive measures. Moreover, MCI diagnosis frequency in PD patients with RBD (66%, or 35/53) was almost threefold that of PD patients without RBD (23%, or 9/40).

The presence of more severe cognitive decline in PD patients with RBD has been supported by other studies showing more specific brain anatomical and functional changes in PD patients with RBD. Indeed, several studies using waking quantitative EEG, event-related potentials, neuropathological exam, anatomical magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography have reported brain dysfunctions in PD with RBD compared to

PD without RBD and healthy subjects [75, 80, 95–103]. Other studies have identified a distinct clinical subtype in PD related to the presence of RBD, with higher risk for dementia, dysautonomia, freezing of gait, falls, symmetric disease, a non-tremor-dominant PD subtype, and hallucinations [37, 104–112]. Taken together, these results indicate more severe and widespread neurodegeneration in PD patients with RBD, which is related to a more altered clinical phenotype, including the presence of cognitive decline.

34.6 Conclusion and Further Directions

Cognitive impairment is a major feature of iRBD, and it increases the risk of developing DLB. iRBD patients with MCI present a more severe and widespread pattern of impaired brain functioning, which suggests underlying neurochemical and neuroanatomical correlates. Patients with PD and concomitant RBD are at higher risk for cognitive decline. Thus, both iRBD patients with cognitive impairment and PD patients with RBD should receive targeted medical attention to better detect and monitor impairment and to enable the development of management interventions for cognitive decline and its consequences.

Future studies on cognition in iRBD should use a greater variety of tests to more deeply assess a wider range of language components (e.g., naming, reading, writing, understanding, and pragmatism) and higher executive functions (e.g., planning, problem solving, inhibition control) as well as procedural learning, judgment capacities, praxis, gnosis, and activities of daily living. Neuroimaging studies could investigate the presence of different patterns of neuroanatomical and neurochemical dysfunction underlying cognitive impairment in iRBD. In addition, the effectiveness of diverse management interventions for cognition, for example, cognitive training, physical exercise, and neuroprotection agents, should be tested in iRBD patients in the near future.

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Neuropsychological Aspects: Impulse-Control Disorders and Other Neuropsychiatric Features in RBD

35

Maria Livia Fantini, Franck Durif, and Ana Marques

35.1 Introduction

Shortly after the first description of REM sleep behavior disorder (RBD) in humans by Schenck and collaborators in 1986 [1], it became clear that the disorder was not just a parasomnia but rather a marker of a multifaceted neurological condition. Indeed, RBD was first shown to predate the development of an alpha-synucleinopathy such as Parkinson's disease (PD), Lewy body dementia, and multiple system atrophy [2]. Then, a number of neurophysiological and neuropsychological abnormalities began to be detected in patients with idiopathic RBD (iRBD), as a possible sign of an impending neurodegenerative process. These include olfactory [3] and autonomic impairment [4], subtle motor signs, as well as color vision impairment [5], cognitive deficits [6, 7], and EEG slowing [8]. Most recent follow-up data indicate that up to 90% of iRBD patients develop an alpha-synucleinopathy at 14 years from the time of RBD diagnosis [9, 10].

RBD is also found in approximately 60% of patients with idiopathic PD. Converging evidences indicate that PD patients with RBD (PD-RBD+) are more severely impaired in both motor and non-motor domains compared to those without RBD (PD-RBD−). Indeed, PD patients suffering from RBD usually show more severe motor symptoms, including more akineto-rigid rather than tremor

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forms, more axial symptoms (including postural instability with falls, freezing of gait, dysarthria), and motor complications (motor fluctuations and levodopa-induced dyskinesia) [11, 12]. They also have increased non-motor symptoms such as greater autonomic impairment [13, 14], worse cognitive performances [15], and increased risk for dementia [16].

The pathophysiology of RBD is thought to be related to a dysfunction of brainstem glutamatergic and/or glycinergic areas involved in REM sleep motor control, including the pontomesencephalic sublaterodorsal nucleus and the ventral medulla inhibitory neurons [17, 18].

However, RBD in PD appears to be a marker of a more widespread and aggressive neurodegenerative process [19, 20], reflecting in part a more severe dopaminergic denervation, as well as a more severe impairment in cholinergic and perhaps serotoninergic and noradrenergic transmission [21, 22].

It is increasingly recognized that PD may be preceded by, and is frequently accompanied by, a wide range of cognitive and neuropsychiatric symptoms, including depression, anxiety, apathy, and impulse-control disorders. The high frequency of these disorders led to a recent conceptualization of PD as a quintessential neurocognitive psychiatric disease [23]. Surprisingly, very little is known about the neuropsychiatric features in RBD, either idiopathic or associated with PD. Tables 35.1 and 35.2 illustrate the main results of studies assessing neuropsychiatric features in iRBD, as well as in PD with RBD compared to PD without RBD.

35.2 Apathy and Depression

Since the very first observations, Schenck and collaborators highlighted the "placid and mild-mannered" temperament of these patients that strikingly contrasted with the aggressive and often violent nocturnal dream enactment behaviors [41]. Later on, one study showed a lower level of daytime physical aggressiveness, as measured by the Aggression Questionnaire, in iRBD compared to sex- and age-matched controls, despite an increased aggressiveness in dreams [42]. Another study investigated dream content and patients' personality traits through the Thematic Apperception Test in 12 patients with iRBD compared to 12 healthy controls. While the study failed to find an increased aggressiveness in dreams in iRBD (though more than 80% of patients were treated with clonazepam at the time of the study that could have decreased dream aggressiveness), a higher passivity level was found to characterize the waking temperament of patients compared to controls [43].

According to the authors, the peaceful and "mild" temperament could be interpreted as an early subtle sign of apathy that commonly occur in the context of neurodegenerative disorders, especially PD, often preceding by many years the motor signs, but no specific measures of apathy were performed in those patients.

Interestingly, in a recent study assessing neurodegenerative markers in a sample of 456 elderly subjects gathered from the general population, subjects with probable iRBD (i.e., iRBD assessed by questionnaire) were found to have more apathy, depression, and anxiety than controls [26]. Another study found increased apathy in

Table 35.1 Studies assessing neuropsychiatric features in idiopathic RBD

Study	RBD vs. HC	RBD diagnosis	Depression	Apathy	ICDs	Other psychiatric disorders	Personality traits	Addictive behaviors (alcohol/smoke/ caffeine)
Postuma et al. [5]	68 vs. 36	VPSG	–	–	–	–	↑ *Harm avoidance in RBD* (Tridim PQ)	–
Sasai et al. [24]	53 vs. 49	VPSG	–	–	–	–	No difference (NEO-PIR: 5 domains, 30 facets)	–
Postuma et al. [25]	347 vs. 347	VPSG	–	–	–	–	–	↑ *Smoking in RBD*, no difference in alcohol and caffeine
Mahlknecht et al. [26]	21 vs. 435 or 35 vs. 421	RBD-SQ or RBD-I	↑ *In RBD* 0.0% vs. 12.6% OR 2.99	↑ *In RBD* 30.8% vs. 13.2% OR 2.95 or 30.3% vs. 12.7% OR 3.15	–	↑ *Anxiety in RBD* 20.0% vs. 6.5 OR 3.65 or 18.2% vs. 6.2% OR 3.42	–	–
Vilas et al. [21]	72 vs. 71	VPSG	↑ *In RBD* 44.4% vs. 18.3%, $p = 0.001$	–	–	–	–	–

(continued)

Table 35.1 (continued)

Study	RBD vs. HC	RBD diagnosis	Depression	Apathy	ICDs	Other psychiatric disorders	Personality traits	Addictive behaviors (alcohol/smoke/ caffeine)
Aguirre-Mardones et al. [27]	44 vs. 40	VPSG	31.0 vs. 15.0 (ns)	↑ *In RBD* 27.3% vs. 10. 3%, $p = 0.04$	–	Overall psychiatric disorders: 34.1% vs. 17.5% (ns)	–	Current smoking, 15.9% vs. 5% (ns)
Wong et al. [28]	724 vs. 12060	RBD-HK	–	–	–	–	–	Smoking, alcohol, and caffeine consumption not associated to pRBD
Baig et al. [29]	128 vs. 292	VPSG	–	–	32% vs. 21% (QUIP-SF) *p* not showed	–	*Idiopathic RBD:* ↑ *neurotic* (OR: 3.07) ↓ *extraverted* (OR 0.65) ↓ *open* (OR 0.49) Big Five Inventory	↑ *Smoking in RBD* than CTRS, no difference for alcohol or caffeine
Barber et al. [30]	88 vs. 33	VPSG	–	↑ *in RBD* 46% vs. 3%, $p = 0.008$		–	–	–

ICDs impulse-control disorders, *VPSG* video-polysomnography, *RBD-SQ* RBD screening questionnaire, *RBD-I* RBD Innsbruck inventory, *RBD-HK* RBD Hong Kong, *Tridim PQ* Tridimensional Personality Questionnaire, *NEO-PIR* NEO Personality Inventory Revised, *QUIP* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, *ns* not significant

Table 35.2 Studies assessing neuropsychiatric features in PD-RBD+ compared to PD-RBD−

Study	PD-RBD+ vs.PD-RBD−	RBD diagnosis	Depression	Apathy	ICDs	Other psychiatric comorbidities	Personality traits	Addictive behaviors alcohol/ smoking/ caffeine
Gjerstad et al. [31]	34 vs. 197	SSQ	No difference (BDI score)	–	–	–	–	–
Postuma et al. [14]	21 vs. 15	VPSG	No difference (UPDRS I)	No difference (UPDRS I)	No difference (clinical interview)	Paranoia : 3 vs. 0, ns	–	–
Romenets et al. [32]	54 vs. 44	VPSG	↑ *In PD-RBD+* $p = 0.009$ (UPDRS I)	No difference (UPDRS-I)	No difference (clinical interview)	No difference in paranoia or hallucinations	–	–
Sixel-Doring et al. [12]	247 vs. 210	VPSG	–	–	–	↑ *In PD-RBD+* Overall psychiatric disorders ($p = 0.026$)	–	–
Fantini et al. [33]	106 vs. 110	RBDSQ + RBD1Q	↑ *In PD-RBD+* HADS score	–	↑ *In PD-RBD+ OR: 4.8*	–	–	–
Kim et al. [34]	578 vs. 366	Clinical interview	–	–	↑ *In PD-RBD+* but no difference after adjusting for age and PD duration	–	–	–

(continued)

Table 35.2 (continued)

Study	PD-RBD+ vs.PD-RBD−	RBD diagnosis	Depression	Apathy	ICDs	Other psychiatric comorbidities	Personality traits	Addictive behaviors alcohol/ smoking/ caffeine
Bayard et al. [35]	31 vs. 67	VPSG	–	–	No difference	–	–	–
Rolinski et al. [36]	224 vs. 251	RBDSQ	↑ *In PD-RBD+* BDI score $p < 0.001$	↑ *In PD-RBD+* UPDRS I $p = 0.008$	↑ In *PD-RBD+* QUIP score if RBDSQ cutoff ≥8	↑ In *PD-RBD+* hallucination and anxiety	–	–
Jacobs et al. [37]	98 vs. 91	VPSG	–	–	–	–	–	↑ *Smoking in PD-RBD+ (OR:1.96)*; no difference in alcohol and caffeine
Baig et al. [29]	Not mentioned ($n = 941$ PD)	RBDSQ	–	–	–	–	*PD-RBD+*: ↑ *neurotic* (OR: 2.02) ↓ *agreeable* (OR 0.71) ↓ *conscientious* (OR 0.69) Big Five Inventory	*No difference* (trend ↑ smoke in PD-RBD+ OR 1.33, $p = 0.06$)
Bellosta Diago et al. [38]	26 vs. 47	RBDSQ	–	–	↑ In *PD-RBD+* QUIP score	–	–	–

Ramirez-Gomez et al. [39]	255 PD	RBDSQ	–	–	↑ *RBD* in PD-ICD vs. PD-noICDs (27% vs. 12%) OR for ICDs: 4.5	–	–	–
Fantini et al. [40]	80 PD (40 ICDs vs. 40 noICDs)	VPSG	–	–	↑ *RBD* in PD-ICD (85% vs. 52%) OR for RBD: 4.9	–	–	–

ICDs impulse-control disorders, *SSQ* Stavanger Sleepiness Questionnaire, *VPSG* video-polysomnography, *UPDRS-I* Unified Parkinson's Disease Rating Scale-part I, *RBD-SQ* RBD screening questionnaire, *RBD1Q* RBD single question, *HADS* Hospital Anxiety and Depression Scale, *BDI* Beck Depression Inventory, *QUIP* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, *ns* not significant

a group of 44 PSG-confirmed iRBD patients compared to 40 age- and sex-matched controls [27], with no difference in depression and anxiety. However, unfortunately in both studies, those neuropsychiatric symptoms were assessed by a single item derived from the Non-Motor Symptoms Questionnaire [44], as studies were not specifically designed to explore neuropsychiatric features. More recently, a study specifically investigated apathy in 88 PSG-confirmed iRBD, 65 PD patients, and 33 controls by means of the Lille Apathy Rating Scale (LARS) [30]. LARS is a recently validated scale that explores nine domains reflecting the main clinical manifestations of apathy, namely, reduction in everyday productivity, lack of interest, lack of initiative, extinction of novelty seeking and motivation, blunting of emotional responses, lack of concern, poor social life, and diminished social awareness [45]. This scale has been found to have a good validity to discriminate between apathy and depression and to determine the severity of apathy [46]. In that study, a total of 46% of iRBD patients were found to be apathetic, compared to 31% of PD and 3% of control participants. However, the proportion of PD patients who had a concomitant RBD was not provided in that study, and it is not known whether RBD would be associated to apathy in the PD population.

Apathy is defined as a condition of decreased motivation leading to a reduction in goal-directed behaviors, interest, or emotion that cannot be attributed to diminished level of consciousness, cognitive impairment, or emotional distress [47, 48].

Apathy can herald the onset of the first motor symptoms in PD or even predate motor symptoms [26]. In early-stage PD, apathy is found in 20–36% of untreated PD patients and usually improves after initiation of dopaminergic treatment. Its frequency, however, increases as the disease progresses, affecting about 40% of patients without dementia and 60% of patients with dementia 5–10 years after the disease onset [49]. Indeed, in non-demented PD patients, the presence of apathy was shown to predict cognitive decline and dementia over time [50].

In order to ascertain whether apathy and depression are associated with RBD in PD, we recently compared 52 non-demented PD-RBD patients and 26 age- and sex-matched PD without RBD patients (unpublished data). Participants underwent a one-night vPSG, followed by an extensive neuropsychological examination, assessing a broad spectrum of cognitive domains. Apathy was assessed by the Lille Apathy Rating Scale (LARS) [45], while depression was assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS) [51]. The study found that, compared to PD without RBD, PD-RBD patients had a higher overall apathy ($p = 0.01$), a lower initiative ($p = 0.004$), and a reduced novelty seeking ($p = 0.001$), and the same findings remained significant after adjusting for sex, duration of the disease, disease severity, treatment dose, depression, and cognitive functions. Interestingly, we found a significant correlation between the degree of apathy and measures of REM sleep without atonia in the whole sample (initiative, $r = 0.43$, $p = 0.003$; novelty seeking, $r = 0.35$, $p = 0.02$, respectively).

In PD, cluster analysis studies have revealed that apathy is associated with male gender, more severe motor symptoms (especially levodopa-induced dyskinesia) [52, 53], worse executive dysfunction [54], and a higher risk of developing dementia [50]. Intriguingly, the same associations have been observed for RBD in PD, suggesting a substantial overlap between RBD and apathy symptoms [55].

Little is known about whether RBD is associated with an increased frequency of depression. Surprisingly, scant and discordant results have been reported about depressive symptoms in iRBD, although iRBD and depression may both represent premotor symptoms of PD. Indeed, depression was found to be significantly associated with probable iRBD in a recent population-based study [26], although another study failed to find this association [27]. Hypoechogenicity of the brainstem raphe, combined with hyperechogenicity of the substantia nigra, was recently found to predict depression in iRBD [21], indicating a possible serotoninergic dorsal raphe dysfunction in the pathogenesis of depression in these patients. In PD, higher scores of depression have been occasionally found in patients with RBD in some studies, but not in other studies [14, 31–33, 36]. The topic of RBD associated with psychiatric disorders and the use of antidepressant medications is covered in depth in Chap. 10.

35.3 Personality Profile of RBD

Personality traits have been rarely investigated in RBD. Postuma et al. found higher scores on harm avoidance in 68 patients with iRBD compared to controls using the Tridimensional Personality Questionnaire [5], but personality differences at baseline did not predict future conversion to PD. However, Sasai et al. were unable to replicate these findings in an independent cohort of 53 patients with iRBD and 49 healthy controls using a five-factor model (NEO-PIR), perhaps due to insufficient statistical power [24]. Very recently, a study explored personality traits in 128 vPSG-proven iRBD, 941 early PD patients (e.g., within 3.5 years of diagnosis), and 292 healthy controls by means of the Big Five Inventory. This is a self-rated questionnaire that follows evaluating personality traits according to the five-factor model: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience. Both iRBD and PD patients showed a similar pattern of personality changes characterized by being more neurotic, less extroverted, and less open to experience compared to healthy controls, with PD-RBD+ showing higher neuroticism than PD-RBD− [29].

35.4 Addictive Behaviors

Recent studies looked at the possible association between RBD and addictive behaviors, particularly impulse-control disorders (ICDs).

Results on addictive behaviors in iRBD are puzzling. Indeed, in a multicenter case-control study investigating risk factors associated with iRBD in 347 patients, iRBD patients were found to smoke more than controls, with no difference in alcohol or caffeine use [25]. In contrast, a large community-based study using a screening questionnaire to diagnose probable RBD did not find such an association with smoking [28], but this may be due to misclassification due to the assessment method. A more recent study did replicate the finding that iRBD patients did smoke more

and were more likely to have smoked in the past, compared to either control subjects or a PD population [29]. This is somewhat surprising when considering the substantial body of evidence indicating a lower frequency of addictive behaviors in PD patients (and the potential protective role of smoking in PD). Interestingly, in the aforementioned study, PD patients as a whole (with and without RBD) had a low rate of addictive behaviors as they smoked less and had a lower alcohol use than controls, but PD patients with RBD were found to have a modestly higher rate of smoking than those without, although this difference was not statistically significant [29]. Actually, an increased frequency of regular smokers in PD-RBD+ compared to PD-RBD− was found in a cohort of 189 PD patients with and without vPSG-confirmed RBD [37]. This may provide further support for PD heterogeneity with possible behavioral changes associated with the "RBD phenotype." Future studies should take into account the duration of iRBD (along with age and gender) in the research patients for the data analyses, since iRBD is now considered to be an evolving prodromal phase of an alpha-synucleinopathy, and so the stage in the evolution of disease may play an important role with the manifestation of any detected addictive behaviors.

35.5 Impulse-Control Disorders

Impulse-control disorders (ICDs) are an increasingly recognized psychiatric complication in patients with Parkinson's disease (PD) treated with dopaminergic agents [56]. They comprise compulsive and repetitive behaviors that are excessive and/or harmful to oneself or others and include compulsive gambling, sexual behaviors, eating, shopping, as well as punding, excessive hobbyism, and overuse of dopamine agents, known as dopamine dysregulation syndrome [57]. The estimated prevalence of ICDs in PD is about 14% or higher according to other reports [58, 59]. Several factors are associated with a higher risk of ICDs in PD, including young age, male sex, previous history of psychiatric disorders, and high doses of dopamine agonists [57].

Recently, we assessed the frequency of ICDs symptoms in a sample of 216 patients with PD, with and without probable RBD [33]. A higher proportion of one or more current ICD symptoms was reported in PD-RBD+ compared to PD-RBD− (53% vs. 28%; $p = 0.0002$). In a multivariate regression analysis accounting for gender, age of onset, PD duration, PD severity, depression score, and total and dopaminergic agonist-LEDD, RBD was associated with a relative risk of 2.59 for any ICD symptom only ($p = 0.001$). In particular, PD-RBD+ had a more than fourfold risk for symptoms of pathological gambling (relative risk [RR], 4.87, $p = 0.049$) compared to PD-RBD−.

Subsequently, a similar study performed in a smaller sample of PD patients replicated these results [38]. However, two studies using either questionnaire or standard criteria to diagnose both RBD and ICDs failed to observe this association. More specifically, a study performed in a cohort of 944 PD patients found an increased frequency of ICDs in PD with probable RBD compared to those without

RBD, but the difference failed to reach significance after adjusting for age and disease duration [34]. This study assessed ICDs using a modified version of the Minnesota Impulsivity Disorders Inventory, instead of standard diagnostic criteria, which doesn't take into account the whole spectrum of ICDs, leading to their possible underestimation. On the other hand, the only study assessing ICDs in PD patients with and without vPSG RBD failed to find an association between ICDs and RBD [35]. Nevertheless, an overall low rate of RBD was found in this cohort (31%) compared to other studies [12, 14], and only 21 patients with ICDs were included. More recently, in a study evaluating motor and non-motor features in a sample of 475 PD patients, participants with questionnaire-assessed RBD were more likely to report symptoms of punding (4.0% vs. 10.0%, $p = 0.02$) and of dopamine dysregulation syndrome (2.4% vs. 7.8%, $p = 0.01$) when using a more stringent cutoff that increased the specificity of the RBD screening questionnaire [36]. More recently, a Latin American multicentric study also confirmed an association between RBD and ICD in PD in a cohort of 255 PD patients. Indeed, probable RBD was found in 37% of PD with ICDs compared to 12% PD without ICDs ($p < 0.001$). Furthermore, the history of REM sleep disorder was associated to an increased risk to develop ICDs (OR = 4.37; 95% CI, 2.26–8.45) [39].

Differences between studies may be ascribed to insufficient power, insufficient percentage of patients with ICDs, as well as incomplete age- and sex- and severity-matching between groups.

We recently sought to assess the frequency of RBD in 40 PD patients with ICDs diagnosed according to standard criteria versus 40 PD patients without any history of ICDs [40].

Participants were recruited among non-demented PD patients consecutively presenting at a movement disorders center at two French and one Italian institutions. We found that vPSG documented RBD was more frequent in PD patients with ICDs compared to those without ICDs (85% vs. 53%, $p = 0.0001$). Furthermore, three out of the six patients with ICDs, who failed to show REM sleep without atonia (RSWA) at vPSG (8% of the total group), reported a typical history of dream-enacting behaviors, with two of them showing brief REM sleep behavioral events (RBE) during vPSG, suggesting a "minor" RBD [60]. This condition was recently shown to represent a "prodromal RBD" in a cohort of PD patients longitudinally assessed over a 2-year period [61]. Thus, when pooling together patients with vPSG-confirmed RBD ($n = 34$) and those with RBE, the cumulative frequency of RBD in patients with ICDs would be raised to 93%. On the other hand, the percentage of RBD found in PD patients without ICDs was close to the one observed in other samples of consecutive PD patients. Furthermore, in a multivariate regression analysis, including age of onset, PD duration and severity, treatment duration, levodopa- and dopamine agonists-equivalent daily doses, and antidepressant use, RBD was still associated with ICDs in PD (odds-ratio, 4.9 [CI=1.3;18.5], $p = 0.02$). These results confirm our previous observation of an association between ICDs and RBD, suggesting that an increased surveillance of symptoms of ICDs should be recommended in PD patients with RBD.

35.6 Decision-Making

Two studies reported impaired decision-making in iRBD patients assessed by the Iowa Gambling Task (IGT) [62, 63]. The first found a deficit in decision-making that was not correlated to the degree of olfactory impairment found in the same patients. However, cognitive functions were not assessed in this study. Another study explored decision-making together with neuropsychological features, including several executive functions such as flexibility, information sampling, categorization, set-shifting, complex problem-solving, as well as impulsivity, in iRBD. Compared to healthy controls, iRBD patients showed a disadvantageous decision-making under ambiguity and did not learn by feedback from the task, despite an integrity of their executive functions. Indeed, a high proportion of iRBD patients showed a lack of consistent strategy, with random or even worse performance observed at the end of the task. The reason for an altered decision-making process in iRBD is not clear. Deficits in decision-making under ambiguity are generally thought to be caused by a dysfunction of the mesolimbic-fronto-striatal loop, which is involved in risk and reward processing. In PD patients, an impaired decision-making has been reported [64], but results are not unequivocal. This has been ascribed to a dysfunctional orbitofrontal cortex resulting from either a dopamine depletion in the ventral striatum or a dopamine overdose induced by the dopaminergic treatment on a relatively spared mesocorticolimbic system [64]. A dysfunctional amygdala, which is implicated in emotion regulation or the presence of executive dysfunctions, has also been invoked to explain decision-making deficits in PD. Nevertheless, no study has assessed whether PD patients with RBD are more impaired than those without RBD.

35.7 Mesocorticolimbic Reward System in RBD

The pathophysiology of neuropsychiatric symptoms in RBD has not been elucidated yet. Since iRBD is thought to be a premotor symptom of PD, one may hypothesize similar changes, perhaps of a lesser magnitude, associated with neuropsychiatric symptoms in PD.

Apathy has been associated with a dysfunction of circuits implicated in reward (the so-called reward system) connecting the orbitomedial and ventromedial prefrontal cortex with the amygdala and nucleus accumbens. Particularly in PD, neuroimaging studies suggest that apathy might result from a dopamine dysfunction in the mesocorticolimbic system, predominantly due to a loss of dopaminergic neurons in the ventral tegmental area (VTA) and leading to impaired emotional reactivity.

On the other hand, behavioral and imaging abnormalities involving the mesocorticolimbic system have also been observed in cases of excessive dopaminergic stimulation, which results in behavioral addictions, such as impulse-control disorders (ICDs).

Accordingly, some authors have postulated that apathy and ICDs would be two opposite motivational conditions belonging to a continuous spectrum of behaviors

ranging from a hypo- to a hyperdopaminergic condition [65]. Both syndromes share abnormal (decreased vs. increased) dopamine receptor stimulation states. Apathy belongs to the spectrum of hypodopaminergic symptoms together with anhedonia, anxiety, and depression, probably resulting from a decreased tonic D2/D3 receptor stimulation, while ICDs are thought to be related to nonphysiological dopaminergic stimulation, especially on D2/D3 receptors, within the mesocorticolimbic system [66].

According to this view, given the presence of apathy and depressive symptoms, a dysfunction of the reward system may be hypothesized in iRBD.

Likewise, since abnormalities of the reward system were found to underlie both apathy and ICDs in PD, our results would point to a dysfunction of the mesocorticolimbic pathway in PD-RBD+ compared to PD-RBD−.

In order to investigate the mechanisms underlying neuropsychiatric abnormalities observed in PD with RBD, we recently explored the activation of the reward system in PD patients with and without RBD by using a functional magnetic resonance imaging (fMRI) paradigm named the "monetary incentive delay task" [67]. The latter explores the reward system during anticipation and reception of a monetary reward, and it has been extensively employed in healthy subjects and in psychiatric patients [68]. Sixty-six participants were included, namely, 22 non-demented PD-RBD+, 22 non-demented PD-RBD−, and 22 healthy volunteers, age- and sex-matched. RBD was diagnosed by vPSG recording. Subjects with ICDs, depression, or apathy were excluded. Brain activation was measured by the BOLD effect, voxel by voxel in the whole brain and in regions of interest (ROI) within the reward system. ROIs were chosen according to independent whole brain analysis: the midbrain, striatum, insula, anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC).

In the whole brain analysis, the reward system was found to be less activated in PD-RBD+ patients compared to PD-RBD− and healthy controls when a reward was anticipated or received. Significant differences were observed in ACC, parahippocampal gyrus, and caudate nucleus ($p < 0.001$ uncorrected). Furthermore, ROI analysis showed a lower activation of the reward system in the PD-RBD+ group during the two different phases of reward. Specifically, during monetary anticipation, the caudate nucleus, insula, ACC, and OFC were less activated in PD-RBD+ group than both PD-RBD− and healthy control ($p < 0.03$). For reward outcome, the nucleus accumbens and OFC were less activated in PD-RBD+ group ($p < 0.02$) compared to the other groups, after adjusting for duration and severity of the disease and dopaminergic treatment dose. In summary, this study found a hypoactivation of the reward system in PD patients with RBD compared to those without RBD, showing for the first time that RBD in PD is associated to abnormalities of the mesocorticolimbic system. These changes may underlie behavioral disturbances such as the increased apathy as well as the increased risk for addictive behaviors and ICDs, which we observed in PD patients with RBD. Perhaps, the same abnormalities may also be related to the impaired decision-making observed so far only in iRBD but possibly present in PD with RBD.

Conclusion

Taken together, these results point to an increased frequency of neuropsychiatric symptoms in RBD. In particular, in patients with Parkinson's disease, RBD seems to be associated with a heavier neuropsychiatric burden, including apathy, depression, addictive behavior, and ICDs.

These changes could reflect a more severe involvement of the dopaminergic mesocorticolimbic pathway involved in the reward process in patients with PD with RBD. Future studies will allow for better ascertaining whether these changes are present at a premotor stage, e.g., in patients with iRBD, and how early in the evolution from iRBD to overt neurodegeneration.

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Biomarkers of Neurodegenerative Disease in Idiopathic RBD

36

Ronald B. Postuma

36.1 Introduction

Arguably the most important implication of the discovery of RBD is that it is associated with an extremely high risk of neurodegeneration. The longest-term studies have suggested that >80% of RBD patients (at least those with onset in middle age) are actually in prodromal stages of neurodegenerative synucleinopathies, namely, Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [1–3]. This is completely unique in the field of neurodegenerative synucleinopathy; for example, in the Movement Disorder Society (MDS) prodromal criteria, idiopathic PSG-proven RBD, with a likelihood ratio of 130, has a predictive value >10× higher than any other clinical marker (i.e., compared to 4 for olfaction and 10 for abnormal motor exam) and >3× any biomarker (the highest biomarker = dopaminergic PET/SPECT at 40) [4].

36.2 Pathophysiologic and Methodological Considerations

RBD is one of many manifestations of prodromal PD. The primary pathologic basis for prodromal PD (and to some extent, DLB) is encapsulated in the Braak staging system [5]. Under this system, PD starts in the olfactory areas and dorsal motor nucleus of the vagus (and perhaps also peripheral nervous tissues in GI tract and the skin). It then progresses along brainstem structures, perhaps via prion-like spread along synaptic connections [6]. At stage II, structures in the pons and lower midbrain are affected, including locus ceruleus and peri-locus ceruleus areas. Only at stage III is the substantia nigra affected. Moreover, because of redundancy in

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dopaminergic motor function, it is not until stages IV and V that patients can be diagnosed with definable parkinsonism, at which point the synucleinopathy has often reached the cortex (and cognitive impairment may occur). This staging system has largely been validated for PD, although it may not fully explain patients who present first with dementia with Lewy bodies. Primary dementia presentations may be due either to alternate pathology pathways (e.g., spreading first to the cortex, as has been proposed in alternate staging models [7]) or to synergism with amyloid pathology, which would dramatically amplify the neurodegenerative effects of even subtle cortical synucleinopathy.

The Braak stage at which RBD occurs is unclear. The obvious candidate stage would be stage II, during which the peri-locus ceruleus area (the human correlate of the sublaterodorsal nucleus) is probably affected [8]. However, it may be that other structures degenerate at earlier stages. For example, the medullary ventral gigantocellular reticular nucleus in a putative indirect pathway of REM atonia regulation (see Chap. 39 and Chap. 42) might be an alternate initial starting point, as it might better explain the long latency between RBD symptom onset and neurodegeneration (which averages 10–15 years in most studies) [9].

36.3 Key Implications of Studying Idiopathic RBD as a Prodromal Marker

Recognition of the spectacularly high risk of neurodegeneration in RBD has led to a concerted effort to identify other markers of prodromal neurodegeneration in idiopathic RBD patients. Study of predictive markers has numerous potential implications. The key ones are:

1. Provide individual counseling for RBD patients—if a reliable marker profile can be generated in an individual, physicians can then provide reliable prognostic information. For example, the clear absence of any other prodromal markers would probably mean that PD/DLB onset may be many years away. On the other hand, documenting olfactory loss and either subtle motor or cognitive abnormalities signals more rapid phenoconversion (see below), which could lead to changes in life planning.
2. Test markers for application to populations other than RBD—studying prodromal synucleinopathy in the general population is made difficult by the fact that despite being the second commonest set of neurodegenerative conditions, PD, DLB, and MSA are still relatively uncommon. Lifetime risk of developing PD by age 80 approximates 2–3%. This implies that in order to prospectively observe 20 persons develop PD in the general community, it would require following approximately 10,000 persons aged 60 for 5 years [4]. By contrast, by following patients with idiopathic RBD, the same number can be observed with only 60 patients.
3. Directly study evolution of prodromal PD and DLB—in clinical medicine, it is rare to be able to directly observe a person develop a new degenerative

syndrome. By prospectively following patients with idiopathic RBD, one can systematically evaluate how long prodromal neurodegenerative markers remain abnormal before diagnosis (i.e., how much lead-time markers can provide in a future prodromal screening program) and how reliable (i.e., sensitive and specific) markers are at different intervals before disease diagnosis.

4. Test markers to stratify patients for neuroprotective trials—there is no group of patients better for a neuroprotective trial against neurodegenerative synucleinopathy than those with idiopathic RBD. This is because they are early enough in the neurodegenerative process that benefit can be measurable and because they are not treated with symptomatic therapy against parkinsonism or dementia (removing the most critical confound in testing neuroprotection in a disease that is treated so successfully symptomatically in early stages). In order to eventually power and plan neuroprotective trials, however, we will need precise estimates of neurodegenerative conversion rates at specific intervals. Given the fact that prolonged (i.e., >5 years) neuroprotective trials are problematic to fund and to run, markers are needed that identify patients who are at relatively short prodromal intervals to defined disease.

A final cautionary note: interpretation of predictive value in long-latency markers is uncertain in RBD. RBD may be more reliable as a model for testing markers with relatively short lead time/latency before manifest parkinsonism or dementia. That is because if the large majority of patients are actually in prodromal stages of neurodegeneration, markers with long latency (e.g., stage I markers such as autonomic dysfunction [10], markers or risk markers such as substantia nigra ultrasound [11] (see below)) may already be abnormal and at a floor by the time a patient presents with idiopathic RBD. This could make it appear that there is no predictive value for neurodegeneration, since both those who convert and those who stay disease-free for several years will already have the abnormal value.

What follows is a summary of what is known about clinical markers and biomarkers of prodromal neurodegenerative synucleinopathy in idiopathic RBD. Please note that studies of cognition, GI motility, other markers of autonomic dysfunction, gait dysfunction, MIBG scintigraphy, and MRI biomarkers have been covered in other chapters, so they will not be discussed here.

36.4 Clinical Markers

36.4.1 Olfaction

Of all prodromal markers for neurodegenerative synucleinopathy (other than RBD itself), olfaction probably has the best evidence for its utility as a prodromal marker. There are now at least seven prospective studies documenting that those with olfactory loss have an approximately four- to fivefold increased risk of developing PD [4]. Olfaction also appears to be a prodromal marker of dementia, including Alzheimer disease and especially DLB [12].

Several studies have investigated olfactory dysfunction in RBD [13–25]. The first was performed by Stiasny-Kolster et al., using Sniffin Sticks. They found that 97% of their cohort had at least one identifiable abnormality (i.e., one of olfactory identification, detection, or discrimination), with approximately 60% testing abnormal on each domain; 56% had at least moderate hyposmia [18]. In the Montreal idiopathic RBD cohort, using the University of Pennsylvania Smell Identification Test, just over 50% of patients tested were abnormal on a relatively strict cutoff (i.e., scores <80% expected values for age and sex) [23]. Moreover, over follow-up in this cohort, olfaction clearly predicts phenoconversion; the 5-year risk of those abnormal on olfactory testing is approximately 60% compared to 20% of those with normal olfaction [26, 27]. Recently the predictive value of olfaction was confirmed by Malknecht et al., who found that abnormal olfaction associated with a sevenfold increase in phenoconversion to defined neurodegeneration [20]. A third study did not find statistically significant predictive value, although the hazard ratio for conversion with abnormal olfaction did exceed 1 (i.e., 1.22) [25]. Note that olfaction is abnormal in PD and DLB, but typically normal in MSA; therefore, it is presumed that olfactory testing will be unable to identify MSA [28].

The lead time of olfaction in the general population is unclear, and some studies have suggested that olfaction only becomes abnormal 0–4 years before motor PD diagnosis [29, 30]. With RBD, we have seen olfactory abnormalities 10 years before PD onset, suggesting latency can often be long. However, there is considerable variability; some patients have had normal olfactory testing as soon as 1 year before neurodegenerative diagnosis (and in 1–2 of our observed cases, olfaction became abnormal only after PD diagnosis). When sloping the progression of olfaction over time and comparing to normal values, the predicted prodromal interval of olfactory abnormalities averages 15 years in our cohort (unpublished data).

36.4.2 Motor Abnormalities

Since neurodegenerative diseases do not start suddenly, it is logical that subtle motor abnormalities should predict parkinsonism. Surprisingly, there is still only very limited evidence of this in the general population, with only one large population-based study documenting this (with a predicted prodromal interval of approximately 7 years) [31]. Within RBD itself, motor abnormalities are commonly observed (gait disorders are covered in Chap. 38) [13, 21–24, 32, 33]. Motor changes are generally relatively mild compared to other prodromal markers, consistent with them being later-stage PD markers. Motor abnormalities have been observed not only with neurological expert exam (using the Unified Parkinson's Disease Rating Scale) but with simpler motor measures that can be performed by a research assistant (e.g., Purdue Pegboard, alternate tap test) [21, 32]. Motor tests are strongly predictive of parkinsonism, regardless of whether it is due to PD or to DLB. Of interest, predictive value is equally good for DLB as it is for PD, and the prodromal motor interval for those who develop dementia first may be even longer than for PD [32]. Overall, the observed interval between the beginning of detectible motor

abnormalities and diagnosed parkinsonism approximates 5–7 years. However, very subtle abnormalities are difficult to detect reliably; it is only 2–3 years before parkinsonism diagnosis that the abnormalities can be detected with >70% sensitivity [32]. Recent studies using vocal analysis have also found that idiopathic RBD patients have measurable vocal abnormalities [33]. These appear to differ from what is typically seen in PD; the predominant characteristic is an articulatory deficit with preserved prosody (in studies by the same investigators, prosody and inarticulate consonants were seen in PD).

36.4.3 Visual Abnormalities

Patients with neurodegenerative synucleinopathy can have impaired vision, related both to retinal dysfunction (e.g., contrast sensitivity) and visuo-perceptual cortical dysfunction (e.g., hallucinations). We have documented abnormal color vision in idiopathic RBD, manifested by a quantitative reduction in ability to sort colors on the Farnsworth-Munsell 100 hue test [19]. Similar findings have also been documented in asymptomatic loss of REM atonia [34]. In RBD, color vision correlates very strongly with cognitive dysfunction, as well as with posterior cortical dysfunction on SPECT scanning, suggesting that the defect is primarily due to impaired visual processing rather than to retinal dysfunction [35]. The color vision deficit in RBD is more severe than found in early PD, suggesting that it may link more closely to primary dementia with Lewy bodies than to PD without cognitive loss (also note that within PD, RBD is associated with a "diffuse malignant" disease subtype characterized by earlier dementia [36], which may also explain this finding).

In prospective follow-up studies, color vision clearly increased risk of phenoconversion to defined neurodegeneration; 60% of those with abnormal color vision converted at 5 years, compared to 25% with normal color vision [3, 27]. The length of the prodromal interval is highly variable. Many patients who convert to PD without mild cognitive impairment at diagnosis will test completely normal even at diagnosis, whereas patients with prodromal dementia are generally abnormal at least several years before.

In terms of other visual abnormalities, a recent study documented that idiopathic RBD patients were more likely to have abnormal pareidolia testing [24]. Pareidolia refers to the tendency to visualize faces where there were none and can be considered as a possible prodrome of visual hallucinations/illusions. We have also tested contrast sensitivity with a handheld iPhone application and have not found abnormalities compared to age-matched controls (unpublished data).

36.4.4 Depression, Anxiety, and Personality

Depression and anxiety are known risk markers of synucleinopathies, and depression and anxiety often overlap. Overall, their relative risk is relatively low (i.e., 1.5–2.5) [4]. In general population studies, there may be a biphasic time course;

there is modest predictive value at long intervals (perhaps reflecting lifelong personality as a risk marker) and then stronger predictive value at short intervals (perhaps reflecting the additive effect of neurodegeneration of mood-regulating brainstem centers) [37].

The link between depression and RBD is complex. On the one hand, depression and anxiety can be prodromal markers of disease. However, antidepressants can trigger manifestations of RBD. Therefore, it is plausible that depression could be associated with either a higher risk of neurodegeneration (i.e., a prodromal manifestation) or alternatively a lower risk (because of inclusion of non-synucleinopathy pharmacologic-caused cases). Several studies have examined if depression is a risk factor for neurodegeneration in RBD. Wing et al. found that RBD patients with comorbid depression were more likely to develop neurodegeneration, with a hazard ratio of 6.7 [38]. In contrast, our group found a lower risk of neurodegeneration in those with associated antidepressant use at baseline [39]. However, those with antidepressant exposure still had clear manifestations of neurodegeneration, which did not differ from those without antidepressants. This may suggest that antidepressants were triggering earlier presentation of RBD in patients who nevertheless had underlying neurodegeneration. In the most definitive study, a multicenter cohort by the International RBD Study Group, there was no association between use of antidepressants and risk of neurodegeneration [3]. It may be that different methods of patient recruitment and different decisions about inclusion of those with antidepressant-associated RBD can explain these differences (see Chap. 10 for more discussion).

There is a well-described Parkinson's disease personality, which is characterized by decreased novelty seeking and increased harm avoidance (i.e., a "conservative" personality) [40]. This may underlie some of the links with reduced smoking and caffeine intake in PD. Similar personality differences have also been observed in idiopathic RBD [23, 41]. However on one prospective follow-up study, personality did not differ between those who developed disease and those who remained disease-free [26]. This may be because personality is a long-standing variable and so is susceptible to the floor effect described above.

36.5 Electroencephalography

In all forms of DLB, including PD dementia, there is general slowing of the electroencephalography pattern, particularly with increased theta and delta power in posterior regions (often with corresponding reductions in fast alpha or beta frequencies). In RBD, several studies have documented similar findings, and even within PD, those with associated RBD have more slowing [42].

The initial description of EEG slowing was performed in 2003 in a study of 15 RBD patients. RBD patients had slowing in the dominant frequency frontal, temporal, and occipital regions during wakefulness and to a lesser extent during REM sleep [43]. Similar slowing was also documented during NREM sleep in a later publication in the same Montreal cohort, which translated into a higher prevalence

of measured slow-wave sleep [44]. This slowing was correlated with mild cognitive impairment in a cross-sectional assessment in this cohort [45]. Sasai et al. in 2013 also confirmed general slowing of EEG dominant frequency in RBD during wakefulness and REM sleep, although this was seen only in "younger" patients (i.e., mean age of 59 years) [46]. This slowing correlated with mild cognitive decline on the Montreal Cognitive Assessment. Sunwoo et al. recently described a pattern of decreased functional connectivity on EEG measures, specifically of the delta band in the frontal lobes, with no other power spectra or locations showing significant effect (see Chap. 30 for discussion of functional connectivity findings on MRI) [47].

So far, only two studies have looked at EEG slowing as a predictor of outcome. Iranzo et al. in a 2010 prospective study found that patients destined to develop new mild cognitive impairment had increased slowing (i.e., delta and theta power) during wakefulness and REM sleep on baseline examination, performed on an average of 2.4 years previously [48]. In 2016, Rodriques-Brazete et al. assessed EEG frequency in 54 patients at baseline and then followed patients for a mean of 3.5 years [49]. Those who eventually developed neurodegeneration had baseline slowing of the dominant rhythm in all cortical areas, compared to those who remained disease-free. This was seen in both those who developed parkinsonism first and dementia first. Using the occipital theta rhythm as a diagnostic test for conversion provided a 79% sensitivity and 77% specificity for predicting outcome.

36.6 Non-MRI Biomarkers

36.6.1 Substantia Nigra Ultrasound

Approximately 80% of PD patients have increased echogenicity of the substantia nigra pars compacta (SNpc) when examined by ultrasound [50]. This is thought to reflect increased iron deposition. Of interest, SNpc hyperechogenicity is present early in PD and does not progress over time, suggesting that it is either a very early prodromal marker that reaches floor by diagnosis or could even be a risk marker. In the SINBAR group, hyperechogenicity was present in 36% of RBD patients (compared to 11% of controls) [51]. A second study found abnormalities in 9/19 (47%) of idiopathic RBD patients [52], and other studies have found a prevalence of 37–63%. Early follow-up of the SINBAR cohort suggested that ultrasound may be predictive (5/8 patients who converted had hyperechogenicity) [53]. However, on longer follow-up, predictive value was limited: only 42% of those who went on to develop defined synucleinopathy had baseline hyperechogenicity, compared to 34% of those who had normal hyperechogenicity [11]. One potential explanation of this absence of predictive value would be the presence of a floor effect and near 100% conversion (i.e., the marker is already maximally abnormal by the time a patient presents with RBD); however, the fact that only 36% had a baseline abnormality makes this somewhat less likely. Therefore, the predictive role of SNpc ultrasound in RBD prediction remains highly uncertain.

36.6.2 Dopaminergic Functional Neuroimaging

Dopaminergic functional neuroimaging can directly assess the dopaminergic innervation of caudate and putamen from substantia nigra. Since approximately 50% of dopaminergic function must be lost before neurodegenerative parkinsonism becomes clinically evident, it stands to reason that subtler loss of dopaminergic function should be measurable. Several studies have documented dopaminergic denervation in idiopathic RBD. The first study, performed by Eisensehr et al. in five RBD patients, found that all patients had some definable deficit compared to controls but of lesser degree than those with defined PD [54]. Subsequent studies by the same group found similar results but also showed a gradient of more loss in clinical RBD than in "subclinical" RBD [55]. Iranzo et al. found an abnormal DAT scan in 40% of subjects with idiopathic RBD; like other studies, abnormalities were found more in the putamen than in the caudate (note that this is the same pattern as PD; however, there have been suggestions that RBD is associated with proportionally more caudate denervation than is typically seen in PD [56]). Abnormalities on dopaminergic imaging also tend to correlate with other predictive findings such as olfaction, mild motor abnormalities, and increased echogenicity on substantia nigra [14, 52].

There are now two prospective studies demonstrating that dopaminergic functional neuroimaging can predict outcome in PD. The first, by Iranzo et al., found that 6/8 patients who converted after 2.5 years of follow-up had baseline DAT abnormality, compared to 11/35 remaining disease-free [53]. Subsequent 5-year follow-up has found that risk of phenoconversion was 33% at 5 years in those with abnormal DAT scan at baseline, compared to 18% among those with normal DAT scan. A second prospective study by Li et al found that among 18 iRBD patients who phenoconverted to parkinsonism or dementia, 12 (67%) had baseline DAT update values below the group median, compared to only 5/17 (30%) of those who remained disease-free [25]. The risk in those with abnormal DAT was increased by 2.3-fold, with annual conversion rates of 15% per year in those with abnormal DAT. These studies are actually the first published studies documenting that abnormal DAT scan predicts neurodegeneration at all (i.e., predating general population studies [57]), illustrating the power/speed advantage of using RBD patients as study models.

36.6.3 Non-dopaminergic Functional Neuroimaging

In addition to dopaminergic imaging, SPECT and PET scanning can also measure brain activity, via proxy assessment of glucose utilization or perfusion. An early study of eight patients with idiopathic RBD disclosed increased perfusion in the pons and decreased perfusion in various frontal and parietal cortical areas [58]. Subsequent follow-up of a larger cohort found similar findings, but also additional increased perfusion/activity in the putamen and hippocampus [35]. These abnormalities correlated with other prodromal markers, such as olfaction and cognitive impairment. A similar finding was seen in a recent 21-patient study, observing increased signal in the

hippocampus and parahippocampus, cingulate, supplementary motor area, and pons and decreased metabolism in the occipital cortex [59]. Another study also found decreased blood flow in the parieto-occipital lobe (precuneus), in addition to the limbic lobe and cerebellar hemispheres [60]. So far, prospective studies are more limited. One study examined hippocampal hyperperfusion (in early stages of DLB, there is hyperperfusion of the hippocampus which reverses as dementia progresses). With prospective follow-up, this was seen in those patients with idiopathic RBD who eventually developed disease but less so in those who remained disease-free [61].

It has recently become clear that neurodegenerative diseases often attack specific networks that are functionally connected (e.g., the default mode network in Alzheimer disease, a basal ganglia network in PD) [62]. In addition to examining individual peaks in perfusion, network-based analyses can disclose general patterns of neurodegeneration. Studies using PET scanning have disclosed a correlated pattern of activity, called the PD network, characterized by increased activity in pons, thalamus, and cerebellum, with reduced activity in premotor frontal cortex and parietal association cortex [63]. This network has also been seen in idiopathic RBD. Moreover the strength of this abnormal network change predicted eventual risk of neurodegeneration in a prospective follow-up [64]. A subsequent study confirmed the existence of the PD network, but also posited a similar more RBD-specific utilization pattern characterized by increased activity in pons, thalamus, medial frontal/sensorimotor cortex, hippocampus, supramarginal and inferior temporal gyri, and posterior cerebellum, with decreased activity in occipital and superior temporal regions (prospective assessment of this is still pending) [65]. Finally, similar findings have been seen on analysis of resting state MRI; abnormality of the resting state MRI basal ganglia network was 96% sensitive and 78% specific in identifying RBD (see MRI Chap. 30) [66].

36.7 Blood/Cerebrospinal Fluid/Tissue Biomarkers

So far, the effort to find blood and cerebrospinal fluid markers of prodromal PD has been unsuccessful. One study of plasma urate found that those who had RBD holding at an idiopathic stage for >5 years may have had higher levels than patients with PD, perhaps suggesting that urate either marks a benign prognosis or is neuroprotective [16]. Otherwise, there are no published studies on blood/cerebrospinal fluid in RBD, which is consistent with the absence of any similar established markers in PD or DLB.

In contrast to blood and cerebrospinal fluid, there is increasing evidence that tissue biopsy may be a key future diagnostic technique in RBD. Studies in established PD have suggested that phosphorylated synuclein can be visualized in the skin and GI tract. In the case of the GI tract, this has been recently documented to occur in prodromal stages of PD. In a Danish national pathology registry, 45% of biopsy samples in patients who had biopsy with a mean of 7 years before PD onset had positive staining. It should be noted that non-specific staining in the GI tract is common, and the same finding was seen in 26% of control samples [67]. In PD, GI

deposition of synuclein follows a rostral-caudal gradient [68, 69], suggesting that rostral structures such as the submandibular gland should be more sensitive.

There have now been three published biopsy studies in idiopathic RBD. The Barcelona group looked at a needle biopsy of submandibular gland [70]. Twenty-one patients submitted to biopsy, for whom 9 had a successful biopsy (i.e., enough submandibular tissue for analysis). Among these, 8/9 had abnormal phosphorylated synuclein deposition. By contrast, 8 of 12 PD patients and 0 of 26 controls had abnormal deposition. It is notable that the proportion of synuclein deposition was higher in RBD than PD. This is consistent with autopsy studies in which PD patients with associated RBD have more synuclein deposition than those without RBD [71], perhaps suggesting that RBD marks a "synuclein-driven" pathophysiology.

A second study performed colon biopsies to look for pathological synuclein deposition; here, sensitivity was clearly lower, both for RBD (4/17 positive biopsies) and PD (0/19), again suggesting that rostral GI biopsy sites are probably superior [72].

Biopsy of submandibular gland is technically difficult and requires the expertise of surgeons; by contrast, skin biopsies are very simple and require little specialist expertise. A very recent study from Marburg took 5 mm punch biopsies from 4 skin sites in 18 idiopathic RBD patients, 20 controls, and 25 early PD patients and co-stained for Syn-129 (i.e., phosphorylated synuclein) and for PGP9.5 (to identify neurons) [73]. 10/18 (56%) RBD patients had abnormal deposition of phosphosynuclein, compared to 20/25 (80%) with PD and 0/20 controls. Most deposition was in autonomic fibers. Proximal biopsies (i.e., near the paravertebral area) were clearly more sensitive than distal limb biopsies. Moreover, patients with positive biopsies were more likely to have DAT denervation and olfactory loss. If these findings are confirmed, tissue biopsy may become a mainstay in the diagnosis of prodromal PD/DLB. For example, if a synuclein-based neuroprotective agent is eventually developed, it would seem reasonable to confirm abnormal synuclein deposition before embarking upon a lifelong course of preventative therapy.

Conclusions

The field of prodromal synucleinopathy is rapidly advancing with multiple new studies published every month. RBD remains by far the most powerful identifier of prodromal synucleinopathy and therefore is the ideal patient population with which to study early stages of disease. Prospective studies in RBD patients have now discovered the means to diagnose near-certain conversion to defined neurodegenerative disease. Moreover, we are now able to identify those with very high conversion risk over 3–5 years. The critical next step is to start using this new knowledge to perform neuroprotective trials against neurodegeneration.

Note Added in Proof: The following is a pertinent recent study: Mondello S, Kobeissy F, Mechref Y, et al. Novel biomarker signatures for idiopathic REM sleep behavior disorder: a proteomic and system biology approach. Neurology 2018. (in press).

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RBD, Gastric Peptides, and Gastric Motility

37

Marcus M. Unger and Wolfgang H. Oertel

37.1 Introduction/Background

The enteric nervous system is discussed as starting point of the neurodegenerative process in Parkinson's disease (PD) [1, 2]. Epidemiological, clinical [3–5], and histopathological studies [6] indicate that involvement of the gastrointestinal tract precedes the motor phase of PD by years or even decades. Hence, it is not surprising that (similar to what has been shown for other non-motor features of PD) also gastrointestinal signs and symptoms are observed in idiopathic RBD (iRBD) [7, 8]. In addition, phosphorylated alpha-synuclein, a histopathological hallmark of PD, has been described in the enteric nervous system in 4 of 17 patients with iRBD [9]. Another study reported phosphorylated alpha-synuclein staining of transcutaneous core needle biopsy material from submandibular glands [10]: positive staining for phosphorylated alpha-synuclein was detected in 8 of 9 patients with iRBD and in 8 of 12 patients with PD but none of the controls. Even though transcutaneous core needle biopsy is a relatively safe diagnostic technique, the low yield of material containing glandular parenchyma (approximately half of the patients) makes it unlikely that this method is suitable as a screening procedure. Hitherto, it has not been ultimately clarified whether gastrointestinal signs and symptoms and/or histopathological markers can serve as predictors for the progression of iRBD into PD.

Neuropeptides that are produced in the gastrointestinal tract act on gastrointestinal motility and modulate cognition, mood, reward, learning, and sleep (functions that are often disturbed in PD). The secretion of gastrointestinal neuropeptides is regulated by local and systemic mechanisms but also by efferents of the vagal nerve. Clinical and neuropathological studies indicate early involvement of the vagal nerve

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in PD and iRBD. Gastrointestinal motility is frequently disturbed in PD [5]. While constipation is commonly accepted as a frequent feature of PD and iRBD [7], only scant data exist for gastric motility in PD [11–13]. This chapter summarizes data on the neuroendocrine system and gastric motility in iRBD and PD.

37.2 Neuropeptides

Based on the hypothesis that a disturbed vagal output in PD and in patients with iRBD results in a disturbed secretion of gastrointestinal neuropeptides, we investigated the postprandial secretion pattern of ghrelin and pancreatic polypeptide in both patient groups compared to age- and sex-matched healthy controls. Interestingly, patients with iRBD and patients with PD exhibited a similar postprandial secretion pattern of ghrelin and pancreatic polypeptide that was distinct from age- and sex-matched controls [14, 15].

Patients with iRBD ($n = 11$) as well as patients with PD ($n = 39$; 19 of the 39 PD patients were drug-naïve) showed descriptively lower fasting concentrations of ghrelin and a reduced recuperation of ghrelin concentrations in the late postprandial phase [15]. Despite controlling for factors that modulate ghrelin response (e.g., gender, age, body mass index, etc.), the interindividual differences in ghrelin concentrations were very high. As a consequence, ghrelin (as single marker) turned out to be not an ideal biomarker for either iRBD or PD. In addition to total ghrelin concentrations, we also investigated acyl and desacyl ghrelin concentrations in an independent cohort of patients with iRBD and PD (unpublished data): despite descriptive similarities to our first study, we could not show a statistically significant difference for fasting and/or postprandial ghrelin concentrations compared to age- and sex-matched controls. Yet, the descriptive difference was more pronounced for acyl ghrelin concentrations compared to desacyl ghrelin concentrations, pointing to a potential relevance of this subform of ghrelin.

Pancreatic polypeptide is another neuropeptide whose release (in response to food ingestion) is mediated by the vagal nerve [16, 17]. Hence, postprandial pancreatic polypeptide release has been suggested as a test for vagal integrity. We hypothesized that postprandial pancreatic polypeptide release is reduced in iRBD and PD due to the postulated vagal dysfunction in both disorders. Our study that investigated secretion of pancreatic polypeptide in response to a standardized test meal revealed an unexpected finding [14]: postprandial pancreatic polypeptide release was not only intact in iRBD ($n = 10$) and PD ($n = 38$; 19 of the 38 PD patients were drug naïve) but was even enhanced and prolonged in iRBD and drug-naïve PD. The reason for this difference remains speculative: local mechanisms, e.g., enteroendocrine cells that compensate a partially defective brain-gut axis, might account for this unexpected finding. Nevertheless, similar to our findings in the ghrelin study, the postprandial secretion pattern for pancreatic polypeptide was distinct from the pattern observed in matched controls ($n = 18$).

In a nutshell, our data point at a possible pathology in the neuroendocrine system in iRBD and PD, but further research is needed to clarify the causality (i.e., whether

the changes in the neuroendocrine system are cause or effect). In this context, the association between neuroendocrine disturbances and clinical data (appetite, weight loss, rarely craving for food, etc.) needs to be further investigated as well. The interaction is complex and mutual: behavior (food intake) affects the neuroendocrine system, and neuroendocrine peptides (e.g., ghrelin concentrations) influence behavior (feelings of hunger and consecutive food intake).

37.3 Gastric Motility

Bearing in mind the aforementioned similarities between iRBD and PD concerning vagal dysfunction and the neuroendocrine system, we hypothesized that gastric motility is disturbed in both disorders too. While gastric emptying has already been shown to be delayed in PD [11–13], there are no data on gastric motility (emptying, respectively) in patients with iRBD. Using the ^{13}C-octanoate breath test, an established diagnostic procedure that has already been validated in patients with PD [12], we reproduced the findings of other groups that have shown delayed gastric emptying in PD. Gastric emptying measured by the ^{13}C-octanoate breath test was not only delayed in moderately affected patients with PD receiving dopaminergic therapy (n = 18) but already in drug-naïve, very early-stage PD patients (n = 21) [18]. The finding of an altered gastric motility in drug-naïve patients supported the hypothesis that gastric dysmotility in PD occurs independently of a dopaminergic intervention.

Patients with iRBD (n = 13), however, showed a pattern of gastric emptying that was indistinct from age- and sex-matched controls (n = 20). The individual patterns of gastric emptying in iRBD (measured by the ^{13}C-octanoate breath test) did not show an association with other potential prodromal markers of incipient PD (e.g., subtle motor slowing, disease duration of RBD, or pathological findings in dopamine transporter imaging) [18]. Preliminary data indicate that another diagnostic method (real-time imaging of gastric motility by magnetic resonance imaging) is a more sensitive method that detects alterations in gastric motility not only in PD but also in iRBD (own unpublished data).

37.4 Conclusions and Outlook

Gastrointestinal signs and symptoms as well as the histopathological findings from a colonic biopsy study [9] endorse the assumption that iRBD represents a premotor stage of PD. The best evidence exists for an increased prevalence of constipation in iRBD [8, 19]. Data on gastric motility are controversial (normal gastric emptying in iRBD as measured by the ^{13}C-octanoate breath test [18], altered gastric motility index in iRBD patients visualized by real-time MRI (own unpublished data)). The discrepancy between the results of the ^{13}C-octanoate breath test and the results of real-time magnetic resonance imaging in iRBD is (most likely) due to methodological effects: high-resolution visualization by magnetic resonance imaging can detect

subtle changes in gastric motility. These subtle changes might be missed by an indirect method of measuring gastric emptying like the ^{13}C-octanoate breath test. Recently, esophageal dysmotility has been proposed as a potential marker for impaired gastrointestinal function in iRBD ($n = 2$) [20]. Yet, a prospective study in a larger cohort of RBD patients is required to determine the informative value of esophageal manometry in RBD. The reported findings concerning neuroendocrine disturbances are still preliminary and inconclusive. At present, neuroendocrine peptides do not seem to be a suitable biomarker that can detect an underlying neurodegenerative disorder, especially due to the high interindividual variability. Further research is necessary to clarify the relevance of the neuroendocrine system in iRBD.

Considering the fact that some neuropeptides, e.g., ghrelin, have neuroprotective potential [21–25] and considering the fact that ghrelin receptor agonists are already tested in clinical studies for other indications (e.g., constipation), neuropeptides might be of interest for neuroprotective or disease-modifying strategies in iRBD in the future.

Another evolving field concerning the gastrointestinal tract and neurodegenerative disorders is microbiome research. Initial studies in PD and RBD indicate that the microbiota pattern in fecal samples is different from controls [26–29]. Even though the reported patterns are not completely congruent, some important similarities exist between the published studies which point at a pathophysiological relevance of the microbiome in PD. In this context, iRBD represents an ideal cohort to learn about longitudinal changes in the gut microbiome and its relevance for neurodegeneration.

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Gait and Postural Disorders in REM Sleep Behavior Disorder

38

Colum D. MacKinnon, Laila Alibiglou, and Aleksandar Videnovic

38.1 Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by an abnormal increase in skeletal muscle activity during REM sleep (REM sleep without atonia—RSWA) and dream enactment [1]. The pathophysiology of RBD includes the presence of Lewy bodies, the pathological hallmark of an α-synucleinopathy, in brainstem nuclei that control muscle tone during REM sleep [2]. Yet, it is now clearly recognized that the expression of RBD antedates dysfunction and neurodegeneration in multiple neural systems including autonomic, cognitive, sensory, and movement domains. Over the course of 5–29 years, up to 81% of people with RBD develop Parkinson's disease (PD), multiple system atrophy, or dementia with Lewy bodies [3].

The fact that RBD is expressed as an abnormal disinhibition of muscle tone is notable in light of evidence that people who co-express RBD and PD tend to have a phenotype that is characterized by motor symptoms that involve dysregulation of postural tone, in particular, postural instability and gait impairment, an increased

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risk of falls, and a higher probability of developing freezing of gait (FOG). This chapter will provide an overview of the overlap in neural systems that govern the control of REM sleep atonia, postural tone, and locomotion; review evidence that subtle disturbances in gait and postural control are present in RBD, prior to a diagnosis of neurodegenerative disease; and describe the motor phenotype that typically presents with the co-expression of RBD and PD.

38.2 Overlap in the Systems that Control REM Sleep Atonia, Arousal, Postural Control, and Locomotion

A simplified diagram of the systems involved in the control of postural control and gait, sleep-wake cycle, and REM sleep atonia is presented in Fig. 38.1. This diagram is designed to emphasize the overlap in the structures and connections that

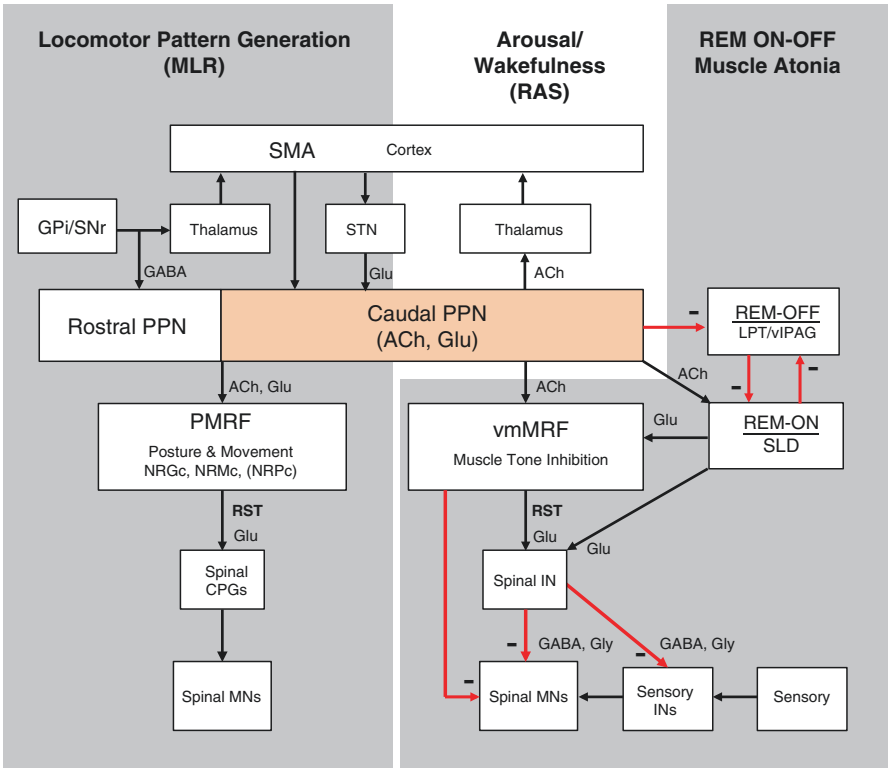

Fig. 38.1 Model of the PPN and how it plays a role in locomotion pattern generation and muscle tone during wakefulness and REM sleep. *ACh* acetylcholine, *CPGs* central pattern generators, *Glu* glutamate, *GPi* globus pallidus internus, *INs* interneurons, *LPT* lateral pontine tegmentum, *MLR* mesencephalic locomotor region, *MNs* motor neurons, *PMRF* pontomedullary reticular formation, *RAS* reticular activating system, *RST* reticulospinal tract, *SLD* sublaterodorsal nucleus, *SNr* substantial nigra pars reticulate, *STN* subthalamic nucleus, *vlPAG* ventrolateral periaqueductal gray, *vmMRF* ventromedial medullary reticular formation

mediate these functions and behaviors. Central to this scheme is the pedunculopontine nucleus (PPN) of the mesopontine tegmentum. The PPN and cuneiform nucleus (CN) comprise the mesencephalic locomotor region (MLR) [4–7]. Stimulation in more caudal regions of the MLR (caudal PPN), an area that has a relatively higher proportion of cholinergic neurons, is associated with suppression of muscle tone via projections to the ventromedial medullary reticular formation [8]. Stimulation in more rostral regions of the MLR (rostral PPN and CN) evokes an alternating pattern of flexor-extensor muscle activity in the legs via cholinergic and glutaminergic inputs to reticulospinal neurons in the medullary reticular formation that project to spinal locomotor pattern generators [9]. Cholinergic, glutamatergic, and GABAergic neurons of the PPN are also part of the reticular activating system (RAS) and play a role in cortical arousal, muscle tone during wakefulness, and REM sleep atonia via projections to the thalamus and REM on/off center in the brainstem, respectively [10–12]. Stimulation of the PPN at high frequency (>100 Hz) suppresses muscle tone [13, 14] but at lower frequency (~40–60 Hz) promotes a transition in thalamocortical cell firing from a state of rhythmic bursting (e.g., during non-REM sleep) to a state of desynchronized firing that characterizes activity during arousal, vigilance, and REM sleep [10–12]. Cholinergic input to the sublaterodorsal nucleus (SLD) (via both M1 and M3 muscarinic receptors) is required for the generation of activity that mediates REM sleep atonia [15]. One of the primary sources of cholinergic input to the SLD is from the PPN [16]. Thus, progressive degeneration of cholinergic neurons of the PPN should result in the emergence of disrupted locomotor pattern generation, changes in postural tone, and the loss of REM sleep atonia. In keeping with this idea, recent studies in nonhuman primates showed that PPN neurons fired relatively slowly at rest, but fired at beta-/gamma-frequencies when the animal was awake, and the same neurons fired at high frequencies when the animal was walking on a treadmill [17]. That is, the same PPN neurons were involved in arousal and locomotor events.

The PPN is considered to be central to the pathogenesis of postural instability, gait dysfunction, and FOG in PD based on its connectivity with the basal ganglia and evidence that neurons in this region degenerate [18–20]. The loss of PPN neurons, in conjunction with increased inhibitory output from the basal ganglia in the parkinsonian state, likely contributes to suppression of MLR function [21, 22]. Levodopa-induced changes in output of the basal ganglia likely explain why dopamine therapies can be effective early in disease (by suppressing the excessive inhibitory input to the PPN), but with disease progression and loss of PPN neurons, these effects diminish. If neurons in the PPN become dysfunctional or degenerate in prodromal phases of PD, as in RBD, then early changes in postural stability, gait, and the coupling of posture and locomotion in PD can be hypothesized.

38.3 Prodromal Changes in Gait and Postural Control in RBD

Evidence from both neuroimaging and behavioral studies demonstrate that subliminal changes in sensory and motor function are present well before conversion from RBD to the clinical manifestation of an α-synuclein-specific neurodegenerative

disorder [23, 24]. In particular, subtle motor dysfunction, olfactory loss, and abnormal color vision are all strong predictors of risk of neurodegenerative synucleinopathy. A limited number of studies have examined measures of movement control, posture, balance, or gait in RBD. Due to the potentially subliminal nature of these signs, particularly in early prodromal stages, it is essential that objective quantitative measures be used. McDade and colleagues examined the spatial and temporal characteristics of gait in patients ($n = 42$) with probable RBD using a gait mat system. They showed that these patients had significantly reduced gait velocity and cadence and increased variability of double support time, stride time, and swing time compared with control subjects. The presence of subtle alterations in the temporal variability of gait in RBD is notable since these measures are less responsive to levodopa and deep brain stimulation therapies in PD and have been suggested to reflect deficits in non-dopaminergic systems that regulate gait rhythmicity [25]. Deficits in the timed up and go (a measure of transfer and gait speed) and repetitive alternate tap test (a measure of bradykinesia and switching) have also been described in people with RBD [24, 26].

We recently examined if RBD is associated with changes in capacity to generate anticipatory postural adjustments (APAs) when transitioning from quiet standing to gait [27]. APAs prior to stepping are characterized by an initial loading of the stepping leg, unloading of the initial stance leg, and a shift in pressure posterior and toward the step leg. This sequence acts to accelerate the center of mass forward and toward the initial stance leg to ensure stability prior to lifting the step leg off the ground. In people with PD, APAs are often absent or have significantly attenuated magnitude and prolonged duration [28–30]. The results of this study demonstrated that APAs were reduced in subjects with RBD in a manner similar to subjects with PD. Moreover, the subjects with RBD showed a distinct abnormality in the shift of pressure late in the gait initiation cycle that is seen in people with PD who have freezing of gait, but not in people without freezing of gait. This finding suggests that pathological changes in systems that control the late phase of gait initiation are present in RBD that may antedate progression to FOG. However, in the absence of a definitive longitudinal study, this idea is purely speculative at this time (Fig. 38.2).

The study by Alibiglou et al. [27] also showed for the first time that the muscle activation pattern observed during gait initiation was abnormal in people with RBD and that this pattern resembles the disturbance in muscle recruitment seen in PD. A hallmark of PD is the presence of a fractionated muscle activation pattern usually consisting of multiple short-duration bursts when making movement to a target, rather than the consistent fused burst of agonist activity seen in healthy adults [31–34]. Figure 38.3 shows an example of the fractionated EMG pattern seen in the tibialis anterior muscle of subjects with PD or RBD. The pathophysiology of the fractionated muscle activation pattern in PD is poorly understood. Abnormal firing patterns in the basal ganglia and motor cortex, impaired reciprocal inhibition at the level of the spinal cord, or alternations in spinal motoneuron excitability could contribute to the abnormal pattern. The latter possibility is supported by studies showing significantly increased variability in the firing patterns [35–37] and changes in the intrinsic excitability of flexor and extensor muscles of the arm [38] in people

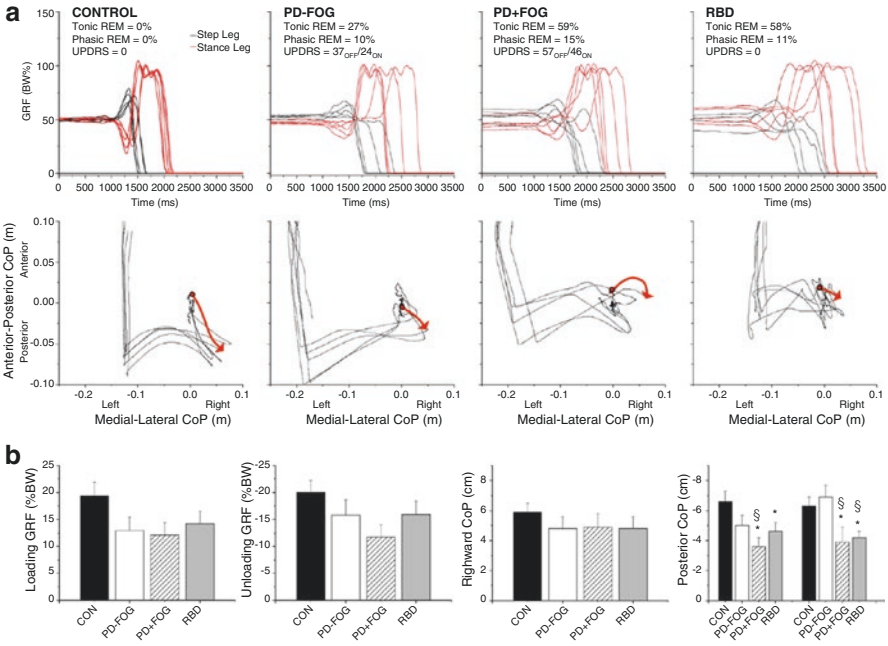

Fig. 38.2 (**a**) Examples of five consecutive trials of self-initiated gait in a participant from each group. The top row shows right (step leg) and left (stance leg) vertical ground reaction forces (GRFs). Each trial has been aligned to the onset of the initial increase in the right GRF at 1000 ms. Note the consistency and smoothness of the profiles in the controls when compared with the presence of multiple inflections, hesitations, and reduced magnitude of the profiles in the PD without freezing of gait (PD-FOG), PD with freezing of gait (PD+FOG), and rapid eye movement (REM) sleep behavior disorder (RBD) participants. The bottom row shows the anterior-posterior and medial-lateral excursions of the net center of pressure excursion (CoP). The red line with an arrow highlights the initial trajectory of the CoP during the anticipatory postural adjustments phase for one trial. (**b**) Changes in the magnitude of the vertical GRFs and the net CoP excursion across groups. Summary of the mean peak amplitudes of the dependent variables across groups during self-initiated gait: (1) stepping leg loading force, (2) stance leg unloading force, (3) peak rightward excursion of the center of pressure, (4) first and second peaks of the posterior excursion of the CoP. *Asterisk* Significantly different from controls at the $P < 0.05$ level. *§*Significantly different from the PD-FOG group at the $P < 0.05$ level. Error bars are 1 standard error. CON, control participants (from reference [27] with permission)

with PD. Descending monoaminergic projections from the caudal raphe and locus coeruleus are the primary sources of regulation of intrinsic spinal motoneuron excitability [39, 40] and provide the capacity to generate self-sustained firing (plateau potentials) in the absence of synaptic input [41]. These intrinsic properties are particularly prevalent in the extensor muscles and are hypothesized to play a role in regulation and maintenance of posture [41]. Accordingly, synucleinopathy of the caudal raphe and locus coeruleus neurons, as is seen in both RBD and PD, would be excepted to alter the firing properties of spinal motoneurons and may contribute to the fractionated EMG pattern observed in both disorders.

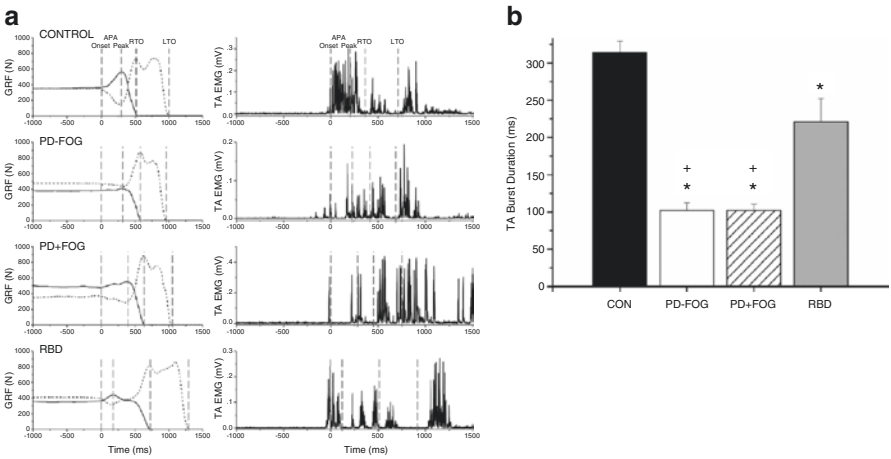

Fig. 38.3 (**a**) Muscle activation patterns in the tibialis anterior (TA) muscle during gait initiation. Representative examples of vertical ground reaction forces (left column) on the stepping (solid line) and stance (dashed line) legs and TA electromyographic (right column) in control (CON), PD without freezing of gait (PD-FOG), PD with freezing of gait (PD+FOG), and rapid eye movement sleep behavior disorder (RBD) participants. Plots have been aligned to the start of the anticipatory postural adjustments at time = 0 ms. Note the fused and prolonged first burst of activity in the TA muscle in the control participants compared to an initial short-duration burst, followed by addition bursts in all other groups. (**b**) Group averages of the mean duration of the first burst in the TA muscle. The first burst duration was significantly reduced in the PD-FOG, PD+FOG, and RBD groups when compared with controls and both PD groups compared with the RBD group. *Asterisk* significantly different from controls at the $P < 0.05$ level. *Plus symbol* significantly different from the RBD group at the $P < 0.05$ level. Error bars are 1 standard error. RTO, right toe-off; LTO, left toe-off (from reference [27] with permission)

38.4 Motor Manifestations in Parkinson's Disease with RBD

Initial descriptions of the phenotype associated with the co-expression of RBD with PD recognized the presence of increased cognitive and autonomic impairment. Subsequent studies that included a thorough clinical evaluation of motor signs found that individuals with PD and RBD were more likely to be of the akinetic-rigid subtype of PD [42–44] and have an increased frequency of falls [42] and a higher frequency of FOG [45]. Currently, it is unclear if the higher incidence of falls relates to deficits in postural control and the increased risk associated with FOG and/or addition of orthostatic symptoms. In keeping with the latter finding, Videnovic et al. [46] showed that individuals with PD and FOG had markedly elevated RSWA compared with those without FOG (Fig. 38.4). In contrast, one other study concluded that RBD was not linked to increased postural instability and gait disturbances in people with PD [47]. This conclusion was based on experiments comparing measures derived from treadmill gait and static and dynamic posturography. Since this study was conducted in the ON medication state, and many of the measures are responsive to levodopa [48], this may explain the absence of a difference between

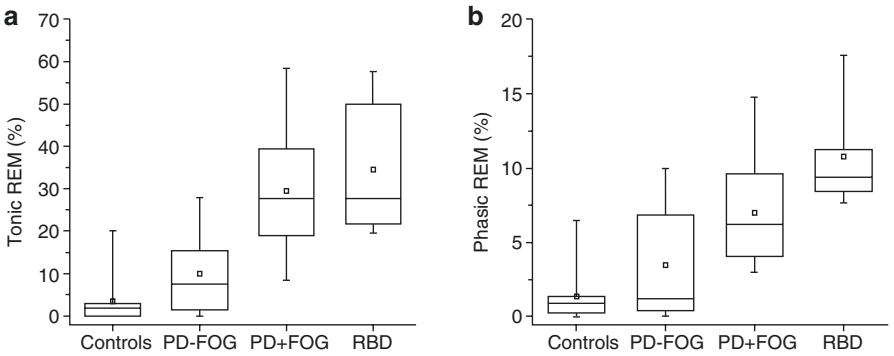

Fig. 38.4 Box and whisker plots of the percentage of REM sleep with (**a**) tonic EMG activity or (**b**) phasic EMG activity. The lower and upper limits of the boxes delineate the 25th and 75th percentiles of the data, the whiskers show the fifth and 95th percentiles, the horizontal line shows the median, and the open square shows the mean within the group. Note the considerable overlap of the distribution of tonic EMG activity between the RBD group and the Parkinson's disease (PD) with freezing of gait group (PD+FOG) (from reference [46] with permission)

PD subjects with and without RBD. Alternatively, their findings may suggest that the presence of RBD is associated with changes in very specific domains of postural stability and gait.

The co-expression of PD with RBD is also associated with changes in cholinergic function. Positron-emission tomography work by Kotagal et al. [49] showed that the PD subjects with RBD had significantly decreased neocortical, limbic cortical, and thalamic cholinergic innervation (estimated from measures of [(11)C]methylpiperdyl propionate acetylcholinesterase). Cholinergic denervation of the thalamus has been shown to be correlated with a history of falls in people with PD [50]. The primary source of cholinergic innervation of the thalamus is the PPN. Taken together, these findings indirectly implicate the PPN as a one of the main sources of dysregulation of muscle tone during both REM sleep and the maintenance of postural tone and stability in the awake state.

Conclusions

Neural circuits that regulate sleep-wake cycles, especially REM sleep, overlap significantly with the circuitry responsible for postural control and locomotion. Emerging evidence suggests changes in locomotion in RBD, which is considered a pre-manifest stage of an evolving α-synucleinopathy. Loss of physiologic muscle atonia during REM sleep has been linked with FOG associated with PD. These findings stem from cross-sectional clinical investigations within the RBD and PD populations. Further longitudinal changes are needed to examine the temporal evolution of these changes along the continuum of the neurodegenerative process. This approach will facilitate better understanding of the pathophysiological processes that underlie gait and postural disturbances in PD and enable the development of biomarkers that will be critical for testing interventions for this large unmet need in PD.

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Part V

RBD: Basic Science

Neural Circuitry Regulating REM Sleep and Its Implication in REM Sleep Behavior Disorder

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39.1 Introduction

Rapid eye movement sleep (REMs) is a distinct behavioral state, originally discovered by the observations of periodically occurring bursts of rapid eye movements during sleep [1]. REMs is also characterized by an activated cortical and hippocampal electroencephalogram (EEG) and concurrent motor atonia. Because of this paradoxical co-occurrence of central activation and peripheral inhibition, REMs is also referred to as paradoxical sleep [2, 3]. Central activation includes cortical and hippocampal activation, reflected in the EEG as low-amplitude high-frequency waves with a dominant 4–9 Hz theta activity (emanating from the hippocampus) during REMs. Muscle atonia, or the loss of muscle tone, occurs in all major skeletal muscles except ocular, inner ear, and some respiratory muscles [4–7]. Atonia during REMs prevents enactment of dreams that typically occur during this stage and therefore protects the animals and humans from self-injuries and injuries to partners resulting from it. When the muscle atonia fails to occur during REMs, humans tend to act out their dreams, and they display a variety of involuntary motor movements ranging from simple jerking and twitching to complex behaviors such as talking, kicking, punching, or jumping from bed. This disorder termed as REM behavior disorder (RBD) was first described by Carlos Schenck and his colleagues at the University of Minnesota in 1986 [8, 9]. In the current chapter, we will summarize the neural basis for REMs generation and atonia and how the dysfunction of the neural circuitry regulating muscle atonia may contribute to the pathophysiology of RBD.

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39.2 REMs Generating Neurons Are Localized in the Pontine Tegmentum

Complete midbrain transections lead to a coma-like state in cats for a few days, but a regular sleep-wake cycle eventually returns, and signs of sleep and wake can be observed from both sides of transections [10, 11]. These observations demonstrated that the isolated forebrain (and the brainstem) is each capable of regulating sleep-wake cycles independently. However, these cats failed to display any forebrain signs of REMs including cortical EEG desynchronization, ponto-geniculo-occipital (PGO) waves, and hippocampal theta waves, but displayed caudal signs of REMs such as periodic muscle atonia. On the other hand, cats with transections at the junction of medulla and spinal cord displayed the forebrain signs of REMs but not muscle atonia [12, 13]. These observations indicate that isolated forebrain is not capable of generating REMs and the brainstem is absolutely necessary for generating this state. When the transections were placed at the junction of the pons and medulla, muscle atonia was still absent while the presence or absence of rostral signs of REMs is still debated. While one study observed REMs-like state with EEG desynchronization and PGO waves [14], another study observed no evidence of REMs after such transections [15]. Thus, the presence of REMs in cats with pontomedullary transections is unclear. However, REMs was completely absent on both sides of the cut in animals with mid-pontine transections or with two transections at both ends of pontine tegmentum [16, 17]. Moreover, periods of pontine spike bursts associated with REMs were still observed in the latter preparation [17] further confirming that the integrity of pontine tegmentum is necessary for REMs generation.

To further localize the REMs generating region within the pontine tegmentum, Carli and Zanchetti performed electrolytic lesions in cats and found that lesions of the pontine region lying ventral to the locus coeruleus, known as subcoeruleus (SC; also referred to as nucleus pontis oralis, or pericoeruleus alpha), largely reduced REMs amounts [18]. As these electrolytic lesions also damaged the fibers passing through this region, it was unclear whether the loss of neurons located in the SC was indeed responsible for REMs suppression. However, neurotoxic lesions that spare the fibers of passage were later performed, and these lesions also produced a significant reduction in REMs, confirming that the neurons responsible for REMs generation are located in the SC in cats [19, 20]. Consistently, electrophysiological studies found that SC contains a population of neurons that fire exclusively during REMs [21–25]. Moreover, injections of a cholinergic agonist, carbachol, into this region produced REMs with the shortest latency compared to any other region in the brainstem, further demonstrating the ability of SC neurons in REMs generation in cats [26, 27].

The exploration for an equivalent region in rats by pontine carbachol injections was not successful as these injections either had no effect on REMs or produced an increase in wake [28]. However, iontophoretic application of GABA antagonists (bicuculline and gabazine) or glutamate agonists (kainic acid) into the pontine region lying ventral to the laterodorsal tegmentum (LDT), referred to as sublaterodorsal tegmental nucleus (SLD) in rats, induced a REMs-like state characterized

by muscle atonia and cortical activation [29, 30]. Consistent with this, neurotoxic lesions of the SLD significantly reduced REMs (~50%) in rats [31]. The reduction in REMs after SLD lesions was accompanied by severe fragmentation (with very short but more frequent REMs bouts), indicating an increased pressure for REMs in these rats [31]. In addition to REMs suppression and fragmentation, SLD lesions produced deficits in muscle atonia [31]. Rats with SLD lesions were unable to maintain atonia and displayed exaggerated phasic twitches and involuntary motor behavior during REMs. The motor behavior ranged from simple jerking and lunging movements to complicated behaviors such as accelerating themselves onto the cages, jumping, and walking. REMs episodes in these rats on many occasions ended after an involuntary flight to the wall or top of the cage [31]. These observations demonstrated that the SLD contains neural elements controlling generation of REMs as well as muscle atonia during this stage.

39.3 Glutamatergic Neurons in the Sublaterodorsal Tegmental Nucleus (SLD) Are REMs Generators

Just like most other brain regions, the SLD is heterogeneous, containing a mixed population of neurons, primarily glutamatergic and GABAergic. Thus, the specific subset(s) of neurons in the SLD responsible for generation of REMs and muscle atonia was unclear. Based on our observations of increased cFos in SLD GABAergic neurons following increased REMs periods induced by acute dark exposure during the light period in albino rats and the glutamatergic nature of the spinal cord-projecting neurons in the SLD, we proposed that these subtypes of SLD neurons are respectively responsible for REMs generation and atonia [31]. However, specific elimination of GABA neurotransmission from the SLD neurons, by genetic deletion of vesicular GABA transporter necessary for packaging GABA into synaptic vesicles, did not alter REMs levels in mice [32]. In contrast, loss of glutamatergic neurotransmission in mice, by genetic deletions of the vesicular glutamate transporter (Vglut2), recapitulated the loss of muscle atonia and REMs reduction observed following SLD lesions in rats [32]. These mice displayed exaggerated phasic muscle twitches and overt motor behaviors including jerking, walking, leaping, jumping, and running while they were in REMs.

These involuntary motor behaviors were distinct from voluntary motor behaviors observed during wake but resembled those observed following SLD lesions in rats as well as humans with RBD [32]. In addition, these mice also displayed significant (c.a. 40%) reduction in REMs amounts and severe fragmentation of REMs [32]. These observations demonstrated that glutamatergic neurons in the SLD are critical elements for the regulation of REMs as well as atonia during this state. Consistent with these findings, Luppi, Fort, and colleagues showed that 84% of the SLD neurons that expressed cFos during periods of increased REMs (after selective REM deprivation) contained Vglut2 and that short hairpin RNA (ShRNA)-mediated deletion of Vglut2 from SLD neurons produced dream-enactment behavior and REM suppression in rats [33]. But, because the SLD neurons that are activated during

REMs did not project to the intralaminar thalamus, which was thought to be involved in cortical activation during REMs, but projected to the ventromedial medulla involved in muscle tone control (see below), Luppi, Fort, and colleagues concluded that SLD neurons are primarily involved in control of muscle atonia during REMs but not in generation of REMs per se [33]. However, dramatic reductions in REMs (40% and 30% decreases in mice and rats respectively) after loss of glutamatergic neurotransmission from the SLD strongly indicate that glutamatergic SLD neurons are necessary for generation of both REMs and muscle atonia during this state.

The rest of this chapter will focus on (1) neural pathways by which the SLD generates REMs and its cardinal signs, such as cortical activation and muscle atonia (other signs of REMs such as autonomic dysregulation, penile erection, and cessation of thermoregulation will not be discussed in this chapter), and (2) neural structures that may control the SLD activity and thereby initiation, termination, and maintenance of REMs bouts before moving on to the neuroanatomical basis of RBD in humans.

39.4 How Does the Pontine REMs Generator, the SLD, Promote Cortical Activation?

Cortically projecting thalamic neurons (thalamocortical system) and their activation by the ascending arousal system (ARAS) were considered critical for EEG desynchronization and behavioral arousal [34–36], and this pathway might also contribute to EEG desynchronization during REMs, as an activated EEG is common to both states. However, large bilateral lesions of the thalamus neither altered sleep-wake cycling nor abolished EEG desynchronization in rats, indicating that the thalamocortical system may have a very limited role in cortical and behavioral arousal [37]. On the other hand, rats with large bilateral lesions of the basal forebrain (BF) displayed monotonous (<1 Hz) EEG activity and were behaviorally unresponsive, indicating that the BF plays a major role in cortical and behavioral arousal [37]. Consistently, optogenetic or chemogenetic activation of BF neurons—cholinergic, glutamatergic, and GABAergic neurons—produced significant and distinct changes in EEG and behavioral arousal [38–40]. While the activation of GABA neurons increased both wakefulness and gamma-band activity ($\gamma = 60–120$ Hz) during wakefulness for several hours [38], activation of cholinergic and glutamatergic neurons only produced EEG changes—an increased theta activity (5–9 Hz) during REMs and suppression of lower-frequency components (<30 Hz) during non-REMs (NREMs) without altering the amounts of sleep-wake [38, 40].

Thus, these results indicate that BF glutamatergic and cholinergic neurons may mediate cortical activation during REMs. Our retrograde tracing studies demonstrated that the BF receives major input from the parabrachial nucleus (PB) and the adjacent precoeruleus (PC) in the dorsolateral pons [37]. Lesions of the PB leads to a coma-like state in rats, and nonspecific activation of all PB neurons or specific activation of glutamatergic neurons in the PB resulted in EEG and behavioral arousal for several hours in rodents, indicating that the PB is a key cell group within

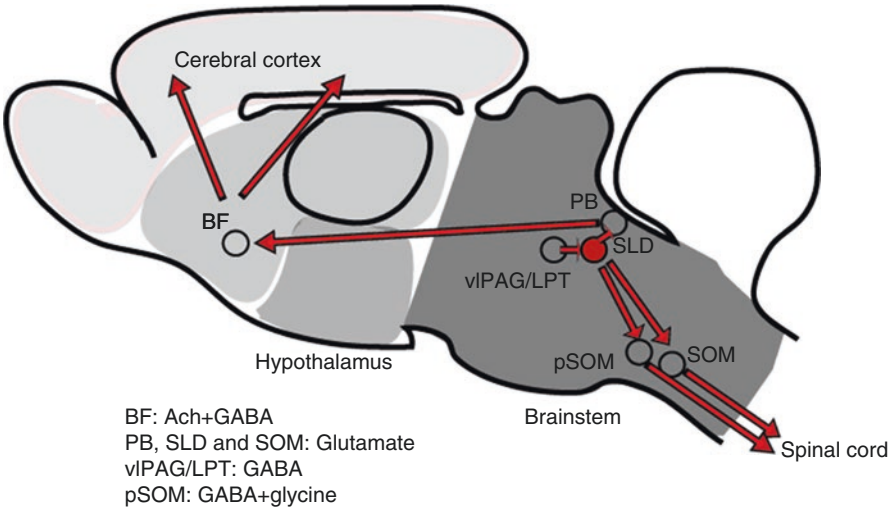

Fig. 39.1 Neural pathways controlling REMs and its cardinal signs. Glutamatergic neurons in the SLD are primarily involved in generation of REM sleep. These neurons may cause cortical activation during REMs by their projections to the PB and BF, whereas they may induce REMs atonia via their descending projections to ventromedial medulla and spinal cord. The inhibitory, presumably GABAergic, neurons in the vlPAG/LPT project heavily to the SLD, and they may "gate" the occurrence of REMs. Subtypes of neurons in each of these regions involved in REMs control are listed below the diagram. *SLD* sublaterodorsal tegmental nucleus, *PB* parabrachial nucleus, *BF* basal forebrain, *SOM* supraolivary medulla, *pSOM* pre-supraolivary medulla, *vlPAG* ventrolateral periaqueductal gray, *LPT* lateral pontine tegmentum, *Ach* acetylcholine

the ARAS that may play a major role in cortical and behavioral arousal [37]. To understand whether the SLD glutamatergic neurons involve the thalamocortical or the PB-PC-BF pathway for EEG activation during REMs, we retrogradely traced the inputs to PB, thalamus (intralaminar thalamus), and BF and found that only the PB-PC complex received inputs from the SLD glutamatergic neurons [41]. Thus, SLD glutamatergic neurons may promote cortical activation during REMs by activating BF neurons (presumably glutamatergic and cholinergic) via a relay in the PB-PC complex (Fig. 39.1).

Similarly, a dominant hippocampal theta rhythm reflected in cortical EEG during REMs has long been known to be generated by septo-hippocampal pathways. Nonspecific neurotoxic lesions of all medial septal neurons, but not specific deletions of cholinergic neurons, abolished hippocampal theta rhythms, indicating that non-cholinergic (primarily GABAergic) neurons in the medial septum (MS) are involved in theta generation [42–44]. Retrograde tracing revealed that the MS receives inputs from PB-PC complex and they are primarily glutamatergic [31]. Consistent with this, neurotoxic lesions of the PC abolished the theta rhythms during REMs [31]. Thus, the SLD glutamatergic neurons may generate hippocampal theta by activating the septo-hippocampal pathways via a relay in PC.

39.5 How Does the SLD Promote Muscle Atonia During REMs?

As discussed earlier, bilateral lesions of the SLD or specific elimination of glutamatergic neurotransmission from the SLD neurons resulted in loss of muscle atonia and involuntary motor movements during REMs in rodents, indicating that SLD glutamatergic neurons are responsible for the generation and maintenance of REMs atonia [31, 41]. Also, classical studies from the laboratory of Michael Chase have shown that REMs atonia is caused by glycine-mediated postsynaptic inhibition of spinal motor neurons [6, 45]. Thus, there must be a relay involving inhibitory premotor and/or interneurons in this atonia process. SLD glutamatergic neurons heavily project to ventromedial medulla (VMM) that contains inhibitory GABA/glycinergic premotor neurons projecting to the ventral horn of the spinal cord, where the spinal motor neurons are located [6, 21, 46–48]. In addition, these SLD neurons directly project to GABA/glycinergic interneurons in the lamina VII of the spinal cord, which, in turn, may inhibit spinal motor neurons. Therefore, SLD glutamatergic neurons may bring about muscle atonia by activating premotor neurons in the VMM and/or interneurons in the spinal cord.

Consistent with this idea, GABA/glycinergic neurons in the VMM expressed cFos during REMs [46–48], and electrical and chemical stimulations of VMM produced muscle atonia [49–53]. Most importantly, neurotoxic lesions of the VMM resulted in REMs without atonia in cats [54, 55]. However, the VMM is a large structure spanning across multiple levels rostro-caudally in the medulla, and the neurochemistry of the VMM reticulospinal neurons differs at rostral and caudal levels. The reticulospinal VMM neurons are predominantly glutamatergic at the caudal level (referred to as the supraolivary medulla, [SOM]), while they are GABA/glycinergic at more rostral levels (referred to as the pre-supraolivary medulla [pSOM]) and at the rostral ventral medulla [RVM]), although both neuronal subtypes are present at all the levels [56]. Neurotoxic lesions restricted to pSOM or SOM, but not RVM, resulted in high-amplitude phasic muscle twitches, myoclonic jerking, and involuntary motor behavior during REMs in rats [57, 58]. Rats with SOM or pSOM lesions displayed vigorous violent motor behavior, often throwing themselves into the air or the wall of their cages while they were in REMs. Termination of REMs episodes often occurs in association with such involuntary flight behavior [57, 58].

Consistent with the neurochemistry, specific elimination of glutamate neurotransmission from the SOM produced increased muscle twitches during REMs, whereas elimination of SOM GABA/glycinergic neurotransmission produced minor effects with fewer high-amplitude muscle twitches during REMs [57]. On the other hand, specific destruction of GABA/glycinergic neurons in the pSOM produced high-amplitude muscle twitches similar to those following VMM lesions in rats [57]. Thus, it appears that GABA/glycinergic neurons responsible for muscle atonia during REMs may present both in pSOM and SOM.

While some of the involuntary motor movements following pSOM/SOM lesions were similar to those following SLD lesions, many of them were distinctively different. For example, coordinated movements such as walking and running were

rarely observed in REMs following pSOM or SOM lesions while they were common after SLD lesions [57, 58]. Also, the number of phasic twitches and involuntary movements during REMs is much lower in pSOM- and SOM-lesioned rats compared to those in SLD-lesioned rats. Finally and most importantly, the tonic or nonphasic atonia was still present after the lesions of SOM or pSOM, whereas it was nearly abolished after SLD lesions. Thus, medullary lesions do not completely mimic the behavioral phenotype following nonspecific SLD lesions or specific loss of SLD glutamate [31, 41, 57, 58]. But, as mentioned earlier, SLD glutamatergic neurons also directly project to spinal cord, where they may activate the GABA/glycinergic interneurons to induce muscle atonia [31]. Consistently, loss of GABA/glycinergic neurotransmission from spinal interneurons resulted in an increased number of phasic twitches in mice, but they were not as robust as those observed following pSOM or SOM lesions [41]. Collectively, this evidence indicates that SLD glutamatergic neurons may orchestrate muscle atonia by activating the GABA/glycinergic neurons in the pSOM and SOM and in the spinal cord (Fig. 39.1). Glutamatergic SOM neurons may further activate the GABA/glycinergic interneurons in the spinal cord to facilitate the muscle atonia (Fig. 39.1). Interestingly, some GABA/glycinergic neurons in the VMM may also contain glutamate, and so these neurotransmitters may operate synergistically to mediate muscle atonia in spinal musculature and suppress motor behavior during REMs.

39.6 Gating and Higher-Order Control of REMs

While the SLD neurons are critical for generating REMs, their activity and, in turn, the generation and termination of REMs are under the control of many other cell groups in the brainstem and the forebrain. Of these sites, ventrolateral periaqueductal gray (vlPAG) and the adjacent lateral pontine tegmentum (LPT) appear to be the most important ones. Pharmacological inhibition of vlPAG/LPT by local infusions of GABA agonist, muscimol, or cell-specific lesions of this region significantly increased both the number and duration of REMs bouts [31, 59–63], indicating that this region may exert tonic inhibitory control over REMs executive neurons in the SLD and thus may "gate" the appearance of REMs. Tracing studies from our lab indicated that GABAergic neurons in this region project extensively to the SLD [31]. These GABAergic neurons in the vlPAG/LPT express cFos after 72 h of selective REM deprivation, indicating that GABAergic neurons in the vlPAG/LPT may act to inhibit REMs [60]. Consistent with this hypothesis, selective activation of vlPAG/LPT GABAergic neurons using chemogenetic methods suppressed REMs for 6–8 h (Vetrivelan R., unpublished observations).

Thus, it appears that these GABAergic neurons inhibit glutamatergic neurons in the cLDT/SLD to suppress REMs and thus form a very potent REM-suppressing system (Fig. 39.1). REM-suppressing vlPAG/LPT in turn receives afferents from many areas in the brainstem (in addition to SLD) and the forebrain. Among these afferents, the preoptic region, lateral hypothalamus (LH), monoaminergic and cholinergic neurons in the brainstem, VMM, and prefrontal cortex are of considerable

importance. Specific neurotransmitter released onto the vlPAG/LPT GABAergic neurons and specific receptors activated may ultimately determine the activity of cLDT/SLD neurons and thus the REMs amount and architecture.

Preoptic region: The importance of the preoptic region in the regulation of sleep has been known for decades [64–68]. The preoptic region contains several cell groups that vary in their projection pattern and neurochemistry. CFos studies have identified two cell groups that are important for sleep regulation—median preoptic (MnPO) and ventrolateral preoptic nucleus (VLPO) [69–71]. Electrophysiological studies identified neurons that are active during NREM and/or REMs in these regions [72–74]. CFos expression and neurotoxic lesion studies helped us further identify the location of neurons that may be involved in REMs control. Many neurons in the medial and dorsal extended VLPO region expressed cFos following periods of increased REMs induced by acute dark exposure during the light period [75]. While lesions of the VLPO cluster decreased both NREM and REMs, lesions restricted to medial and dorsal extended VLPO (eVLPO), without involving the VLPO cluster, decreased only REMs [76]. Thus, the VLPO cluster and the eVLPO may regulate NREM and REMs, respectively. Based on heavy projections from eVLPO to the vlPAG/LPT [77], we speculate that the eVLPO neurons involved in REMs control are presumably GABAergic. Thus, the eVLPO neurons may disinhibit the SLD by inhibiting the GABAergic vlPAG/LPT neurons to promote REMs.

Lateral hypothalamus: In the LH, neurons containing melanin-concentrating hormone (MCH) have been shown to be particularly involved in REMs regulation [78]. These MCH neurons are maximally active during REMs [79], and selective activation of these neurons specifically promotes REMs [80]. MCH neurons send moderate to heavy projections to the vlPAG/LPT [81, 82]. Importantly, GABAergic neurons in the vlPAG/LPT express cFos during REMs suppression induced by pharmacological inhibition of LH indicating that MCH neurons located in the LH may inhibit these neurons to modulate REMs [81]. While the MCH and other neuropeptides, such as cocaine- and amphetamine-regulated transcript and nesfatin-1 present in the MCH neurons, are inhibitory in nature [83–85], MCH neurons also contain an excitatory neurotransmitter, glutamate [86]. Thus, it is also possible that MCH neurons may inhibit GABAergic neurons in the vlPAG/LPT and/or activate cLDT/SLD neurons to promote REMs. Although activation of MCH neurons increases REMs, specific deletion of MCH neurons had no effect, indicating that these neurons are not necessary for spontaneous REMs but may be recruited when the REMs levels need to be increased above baseline, e.g., REM rebound following REM deprivation [80]. Thus, MCH projections to the vlPAG/LPT and the SLD may be particularly important for homeostatic regulation of REMs.

Neurons expressing orexin intermingled with MCH neurons in the LH may play an opposite function in REMs regulation. Orexin neurons fire maximally during wake and minimally during REMs (reciprocal to MCH neurons), and their firing rate is positively correlated with muscle tone [79]. Orexin knockout in mice does not alter REMs levels but leads to cataplexy [87], which is characterized by sudden loss of muscle tone (as occurs in REMs) triggered by positive and other emotions during wake. Thus, it appears that orexin neurons may stabilize wake and prevent

"unwanted REMs" entry into wake [31, 88]. Orexin neurons innervate heavily to the LPT, and these LPT neurons express orexin2 receptors [89]. Neurotoxic lesions in the LPT also caused cataplexy in rats similar to orexin knockout mice [31]. Thus, orexin neurons may contribute to the muscle tone regulation in somatic musculature by its excitatory action on spinal projecting neurons in the LPT, which are primarily glutamatergic [89].

Cholinergic and monoaminergic neurons: A reciprocal interaction model of REMs by McCarley and Hobson [90] proposed cholinergic and monoaminergic neurons in the brainstem as REM-on and REM-off systems, respectively, and the interaction between these two systems as the primary determinant of REMs occurrence [90]. However, as mentioned above, it is now clear that glutamatergic neurons in the SLD rather than pontine cholinergic neurons are critical for REMs generation [41]. The two cholinergic cell groups, the pedunculopontine tegmentum (PPT) and laterodorsal tegmentum (LDT) located in the dorsolateral pons, although initially attracted attention as potential candidates for REMs regulation based on REMs-like state induced by local pontine injections of the cholinergic agonist carbachol, more recent studies negated their role in REMs generation. Although activation of neurons in the PPT/LDT by either electrical stimulation or microinjections of glutamate produced an increase in total amount of REMs in rats [20, 91, 92] and cell-specific lesions of PPT/LDT produced REMs suppression in cats [20], these stimulations and lesions included non-cholinergic neurons in the same region as well as neurons in the surrounding regions. Moreover, injections of higher doses of glutamate into the PPT produced an increase in wakefulness rather than an increase in REMs [92, 93]. Neurotoxic lesions restricted to the PPT or the LDT did not reduce REMs even though these lesions destroyed both cholinergic and non-cholinergic neurons [31].

While early electrophysiological studies have shown that many neurons in the PPT and LDT region are active during REMs [94, 95], recent juxtacellular labeling studies found that all cholinergic neurons in the PPT/LDT region are active both during wake *and* REMs, indicating that these neurons may participate in cortical activation rather than REMs generation [96]. Conversely, selective activation of cholinergic neurons in the PPT using optogenetic methods increased the probability to enter REMs in mice [97]. But, the transgenic mice used in this study release three times more acetylcholine than wild-type mice at baseline conditions, and, therefore, optogenetic stimulation would have resulted in synaptic release of acetylcholine at supraphysiological levels. However, using different transgenic mice that do not suffer from this drawback, Kroeger and colleagues convincingly showed that chemogenetic activation of PPT cholinergic neurons did not alter REMs amounts or architecture but only caused suppression of lower-frequency EEG rhythms during NREMs [98]. Thus, pontine cholinergic neurons may not play a significant role in generation of REMs, but they may just play a modulatory role in certain species, e.g., cats.

The importance of monoaminergic neurons in the regulation of spontaneous REMs is still debated. Noradrenergic neurons in the LC and the serotonergic neurons in the dorsal raphe (DR) display complete cessation of firing just prior to and during REMs [99–101]. As these neurons project to PPT and LDT cholinergic

neurons and may have inhibitory effect on them, it was proposed that monoaminergic neurons may play a permissive role in REMs—in other words, absence of LC and DR neuronal activity may permit REMs to occur [90]. Antidepressants that increase the levels of these monoamines completely suppress REMs, and these observations further substantiate the importance of the monoaminergic mechanism in REMs control. But, selective lesions of noradrenergic neurons in the LC and serotonergic neurons in the DR do not affect REMs levels [31]. Thus, it appears that these monoaminergic neurons may not be critical for baseline control of REMs, but they may modulate the amount and architecture of REMs by acting on the primary REMs control circuitry (REM-on cLDT/SLD and REM-off vlPAG/LPT). Consistent with this idea, we found that REMs suppression induced by antidepressants is accompanied by increased cFos expression in the vlPAG/LPT neurons [102, 103], indicating that vlPAG/LPT may be a potential relay in REMs suppression by the monoaminergic system.

In contrast to noradrenergic and serotonergic neurons, dopaminergic neurons do not seem to be particularly important for REMs regulation. Dopaminergic neurons in the substantia nigra primarily project to the other cell groups of basal ganglia (striatum and globus pallidus), whereas the ventral tegmental area predominantly projects to the nucleus accumbens. These pathways may promote sleep and wake, respectively, but do not appear to be involved in regulation of REMs amounts [104]. In contrast, the A11 dopaminergic cell group in the hypothalamus projects to the pontine REM control center, but selective destruction of these dopaminergic neurons did not influence REMs.

Ventromedial medulla: As mentioned earlier, the evidence for the existence of REMs after transections at pontomedullary junctions has been contradictory. While Siegel and colleagues observed REMs-like state (with EEG desynchronization and PGO spikes but without atonia) [14], Webster and colleagues did not observe any distinctive signs of REMs in cats with transections at the pontomedullary junction [15]. It is likely that REMs was still present (without recordable peripheral signs) in these cats because even the cats with an isolated pons displayed periodic pontine spike activity associated with REMs.

Thus, integrity of the medulla may not be crucial for REMs generation. Nevertheless, neurons that are selectively active during spontaneous REMs or express cFos during periods of increased REMs following selective REMs deprivation were found in the VMM [60, 105], in addition to the SLD, indicating that the VMM may contribute to REMs regulation. Consistently, neurotoxic lesions in the SOM (i.e., VMM lying above the inferior olive at the level of facial nucleus) produced a 40–50% reduction in REMs [57]. Optogenetic activation of GABAergic neurons in the VMM has been shown to initiate as well as extend the REMs episodes [106]. Dual tracing studies identified two sets of GABAergic neurons in the VMM—one projecting rostrally to pons and midbrain and another projecting to the spinal cord—and the rostral projections specifically to the vlPAG/LPT have been shown to be sufficient for initiation and maintenance of REMs [106]. Thus, the VMM GABAergic neurons may promote REMs by inhibiting REM-suppressing GABAergic neurons in the vlPAG/LPT [106].

39.7 Circadian Control of REM Sleep

In addition to homeostatic control, REMs is also under strong circadian control mechanisms. It is well established that the suprachiasmatic nucleus (SCN) serves as a master pacemaker and controls almost all physiological and behavioral rhythms in mammals [107–109]. Lesions of SCN have been shown to abolish body temperature, locomotor activity, and sleep-wake rhythms [110–114]. Recent studies using forced desynchrony protocols have shown that circadian rhythms of REMs can be desynchronized from rhythms in NREMs and that the former is tightly coupled to body temperature rhythms [115, 116]. These studies have also shown that rhythmic clock gene expression in the dorsomedial SCN may orchestrate REMs rhythms [116]. It is still unclear how the dorsomedial SCN is connected to the SLD and contributes to REMs rhythms. On the other hand, it is known that orexin neurons and MCH neurons in the LH may contribute to REMs rhythms. While the loss of orexin neurons decreases the amplitude of REMs rhythms in mice, loss of MCH neurons increases it [80, 117].

These data indicate that balance between orexin and MCH-ergic system may determine diurnal variation and circadian rhythms in REMs [80]. Although MCH or orexin neurons do not receive direct inputs from the dorsomedial SCN, they receive inputs from subparaventricular zone (SPZ) and dorsomedial hypothalamus (DMH), to which the SCN projects heavily [108, 118–120]. Thus, the dorsomedial SCN targets the vlPAG/LPT and the SLD via relays in the SPZ/ DMH and LH, and this pathway may be involved in generation of REMs rhythms.

39.8 Dysfunction of the REM Atonia Circuitry May Be Responsible for REMs Behavior Disorder

RBD is a parasomnia characterized by REMs without atonia (absence of muscle atonia and increased phasic muscle twitches during REMs) and recurrent nocturnal dream-enactment behavior. Humans with RBD display disinhibited motor behaviors ranging from simple jerking to complex behaviors, including falling from bed, jumping, punching, talking, and shouting while they are in REMs. The abovementioned data from animal research provide clues about the potential causes and mechanisms involved in the pathophysiology of RBD. Loss of muscle atonia and dream-enactment behavior observed in animals following SLD and VMM lesions [31, 41, 57, 58, 121] strongly indicate that degenerative lesions in these structures may be potential causes of idiopathic RBD in humans. Consistent with this, stroke, inflammation, or degeneration in the SLD region (although the term “subcoeruleus [SC]” is mostly used to describe the human equivalent of SLD, we still used the term “sublaterodorsal nucleus [SLD]” for consistency and clarity) has been linked to RBD in humans [122–126] (Chap. 9 discusses lesional RBD). However, no such clinical evidence is available to attribute VMM pathology to RBD, which may in part be due to more serious cardiorespiratory abnormalities as well as wake-related motor abnormalities associated with it.

While the pathology of the SLD and VMM may underlie the loss of muscle atonia during REMs, the neural origin of the motor behaviors has been unclear. As the motor behaviors and the involuntary movements correlate with dream content, one longstanding assumption has been that signals from the motor cortex drive those movements, but animal or human data supporting this idea is still lacking. On the other hand, a compelling alternative explanation has been proposed by Blumberg and Plumeau [127] who provided evidence for the brainstem as a source of the pathological movements in RBD and that sensory feedback from moving limbs could be an important influence on the content of dream mentation with dream enactment.

It is also possible to hypothesize that the reticulospinal tracts originating from the midbrain locomotor region (MLR) are involved in the involuntary motor behavior in RBD. But, neurotoxic lesions of MLR result in cataplexy in animals [31], and cataplexy co-occurs with combined narcolepsy type 1 RBD in humans. Interestingly, both cataplexy and RBD occurred in one individual after an isolated pontine stroke [128]. It is likely that this patient had lesions in both the MLR and SLD and involuntary motor movements still occurred during REMs. Thus, motor movements are unlikely to be originated from the MLR. It is still entirely possible that MLR damage may be incomplete in this human case and thus could have contributed to the motor movements in RBD. Sleep studies on the MLR and SLD double-lesioned animals are critical to test this hypothesis.

Another important observation from the animal literature is that bilateral lesions of the SLD produce significant REMs suppression and REMs fragmentation [31], whereas unilateral lesions had no effect on REMs amounts or architecture (Lu. J, unpublished observations). Thus, we predict that RBD patients displaying REMs suppression and fragmentation would display pathology of bilateral SLD and this may indicate further progression of the disease. It is now well established that RBD is linked with other neurodegenerative disorders, specifically Parkinson's disease (PD) and other alpha-synuclein diseases such as multiple system atrophy and dementia with Lewy bodies [126, 129–131]. Following up RBD patients, Schenck et al. found that most of them (81%) developed PD on average 14 years after the onset of RBD [132]. Thus, detailed assessment of REMs architecture would be critical in evaluating the disease progression and PD prognosis. Interestingly, many reports indicate that idiopathic RBD subjects display loss of dopamine activity in the striatum [133], although PD symptoms are not presented at this point. PD symptoms in humans appear only after the loss of ~>70% dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) [134–136]. Hence, it is likely that degenerative changes in the SLD glutamatergic and in SNc DA neurons may begin at the same time and strong compensatory mechanisms in the SNc dopaminergic system might prevent the occurrence of motor deficits associated with PD in the early stages. Thus, RBD and associated REMs changes provide a ~10-year window period for therapeutic interventions to protect the remaining SNc DA neurons.

39.9 Summary Points

- Neurons that are necessary for generating REMs are localized in the sublaterodorsal tegmental nucleus (SLD) in the dorsolateral pons, and they are mostly glutamatergic.
- SLD glutamatergic neurons send descending projections to the ventromedial medulla and spinal cord where they activate inhibitory premotor and interneurons that then inhibit spinal motor neurons to cause muscle atonia during REMs. Neurodegenerative lesions along this pathway may be the fundamental cause of REM behavior disorder.
- SLD glutamatergic neurons project to the basal forebrain through a relay in the parabrachial nucleus, and this pathway is likely involved in cortical activation during REMs.
- Activity of SLD glutamatergic neurons and thereby the generation and termination of REMs are under the control of REMs suppressing neurons (presumably GABA/glycinergic) in the ventrolateral periaqueductal gray (vlPAG) and the adjoining lateral pontine tegmentum (LPT).
- Medial prefrontal cortex, lateral hypothalamus, preoptic region, and ventral medulla as well as pontine monoaminergic systems may control REMs through their projections to the vlPAG/LPT.
- REMs is under strong circadian control mechanisms, and rhythmic clock gene expression in the dorsomedial part of suprachiasmatic nucleus may primarily orchestrate circadian rhythms in REMs.
- REM behavior disorder (RBD) may be due to neurodegenerative lesions along the REMs atonia pathway including SLD and the VMM.
- Assessment of REMs amounts and architecture in RBD patients may provide important clues about the RBD progression into Parkinson's disease.

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Neuropathology of REM Sleep Behavior Disorder

40

Carlos H. Schenck

40.1 Clinical-Neuropathological Study of 172 RBD Cases

A strong foundation for determining the neuropathologic substrates in patients with RBD with or without a coexisting neurologic disorder was established in 2013 with the publication of a multicenter study spearheaded by Boeve [1]. Clinical and neuropathologic findings were analyzed on 172 autopsied cases (the largest published series) from collaborating sites in North America and Europe, from 1990 to 2012, involving patients with video-PSG documented RBD, or with probable RBD (based on a convincing history and/or screening questionnaire results), with or without a coexisting neurologic disorder. These 172 cases were male-predominant, viz., 83% (143/172). The mean ± SD age of onset for the following core features were RBD, 62 ± 14 years (range, 20–93 years); cognitive impairment, 69 ± 10 years (range, 22–90 years [$n = 147$]); parkinsonism, 68 ± 9 years (range, 20–92 years [$n = 151$]); and autonomic dysfunction, 62 ± 12 years (range, 23–81 years [$n = 42$]). Mean age at death was 75 ± 9 years (range, 24–96 years). RBD preceded the onset of cognitive impairment, parkinsonism, or autonomic dysfunction in 51% (87/172) of patients by a mean 10 ± 12 years (range, 1–61 years).

The primary clinical diagnoses among those with a coexisting neurologic disorder were dementia with Lewy bodies (DLB) ($n = 97$), Parkinson's disease (PD) with or without mild cognitive impairment or dementia ($n = 32$), multiple system atrophy (MSA) ($n = 19$), Alzheimer's disease (AD) ($n = 9$), and other various disorders.

The neuropathologic diagnoses were Lewy body disease (LBD) ($n = 77$, including one case with a duplication in the gene encoding a-synuclein), combined LBD

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and AD (n = 59), MSA (n = 19), AD (n = 6), progressive supranuclear palsy (PSP) (n = 2), and other pathologies.

A major finding was that among the neurodegenerative disorders associated with RBD, 94% (160/170) were synucleinopathies. RBD typically preceded the onset of overt synucleinopathy neurodegeneration. This is in contrast to the non-synuclein neurodegenerative disorders, where the RBD typically emerges with or after the emergence of these disorders, as discussed in Chap. 7.

40.1.1 Neuropathologic Assessment

All brains in the cited study [1] were processed, sectioned, stained, and assessed using local neuropathologic procedures. Pathologic findings and diagnoses were characterized using standard stains and criteria, as described [1]. For LBD, cases were classified as brainstem-, limbic-, or neocortical-predominant LBD as suggested by consensus guidelines [2, 3]. However, the data analysis was simplified in grouping together a single LBD postmortem diagnosis.

40.1.2 Results

One case of idiopathic RBD (iRBD) without any clinical neurologic signs or symptoms at the time of death was included [4], to be discussed in the next Sect. 40.2. Seven of the 29 women had MSA and 16 had LBD ± AD. For the predominant disorders found in this series, the male frequency was LBD, 90% (69/77); LBD + AD, 88% (52/59); LBD ± AD, 89% (121/136); MSA, 63% (12/19); and AD, 33% (2/6). Therefore, the strong association of RBD with the synucleinopathies was further substantiated in this clinical-neuropathological study, and the existence of a wider spectrum of disorders that can underlie RBD was also revealed. The high frequency of RBD among males (83%) was present in this series, as with all other series. However, the frequency of RBD among men was lower in MSA (63%). The neuropathological and clinical findings emphasize that when RBD is associated with dementia, parkinsonism, or autonomic dysfunction, then RBD usually predicts an underlying synucleinopathy. Considering all cases in this reported series, the predictive accuracy of a synucleinopathy was 94%, and this increased to 98% when considering only PSG-proven cases.

Although RBD can begin in childhood, adolescence, and early adulthood, the mean age of onset of RBD was 62 years in this series, with over half being in the 50–69-year age range and 80% in the 50–79-year age range. Eleven percent had RBD onset prior to age 50. These findings are consistent with other series showing that RBD is typically a disorder which begins in the 50–80-year age range [5].

When associated with an underlying neurodegenerative disorder, RBD usually begins prior to cognitive impairment, parkinsonism, or autonomic dysfunction (occurring in half of the subjects in this series), yet RBD can emerge during or after the onset of these other neurologic features. The long interval between RBD onset and the onset of cognitive impairment, parkinsonism, or autonomic dysfunction in

many cases was strongly present in this series, with 30 cases having ≥10 years latency intervals and 5 cases having a ≥40 years latency intervals. The presence of RBD in cases with otherwise typical features of AD or CBS should raise concern about the possible presence of comorbid LBD. This point was emphasized with two patients in this reported series [4, 6] who had histories of vPSG-confirmed RBD and clinical AD, without any parkinsonian features ever detected, and yet at autopsy was found to have mixed LBD + AD neuropathology. Furthermore, there has not yet been a reported case of clinical AD with PSG-confirmed RBD that at brain autopsy found no synucleinopathy pathology. On the other hand, RBD at times can be associated with a non-synucleinopathy neurodegenerative disorder, and so the presence of comorbid RBD may dissuade some clinicians from considering the correct underlying neurodegenerative disorder, in these uncommon instances. Therefore, the strong association of RBD with the synucleinopathies is supported by the neuropathologic findings. Finally, in a longitudinal study of idiopathic RBD (iRBD) that documented an eventual 82% conversion rate to a parkinsonian disorder [7], in three patients the antemortem diagnoses of PD and DLB were confirmed by neuropathological examination that found widespread Lewy body pathology in the brain, along with α-synuclein aggregates in the peripheral autonomic nervous system in one case. In these three patients, neuronal loss and Lewy pathology (α-synuclein-containing Lewy bodies and Lewy neurites) were found in the brainstem nuclei that regulate REM sleep atonia.

40.2 Neuropathology of Idiopathic RBD Cases

Two cases of iRBD with neuropathological findings have been reported [4, 8]. The first case involved an 84-year-old Japanese man with a 20-year history of undiagnosed and untreated RBD with recurrent violent behavior during sleep, but no other clinically evident neuropsychiatric disorders [8]. vPSG study confirmed the diagnosis of RBD, and RBD was controlled with bedtime clonazepam. He died from pneumonia 2 years later, at age 86. Neither parkinsonism nor dementia was ever detected. Histopathologic examination revealed LBD with a marked decrease of pigmented neurons in the locus coeruleus (LC) and substantia nigra (SN). These histologic findings represented the first documented evidence of a loss of brainstem monoaminergic neurons in iRBD and raised the compelling question as to whether LBD might provide the explanation for iRBD in the aged.

The second case involved a 72-year-old man with a 15-year history of iRBD, confirmed by vPSG [4]. Clonazepam therapy at bedtime controlled his dream-enacting behavior. No neurologic dysfunction was ever detected in the motor, cognitive, and autonomic domains during serial neurological examinations within this 15-year period. He died from pneumonia. Histopathology detected LBD, but the LC and SN did not have significant neuronal loss or gliosis, despite the presence of Lewy bodies. Also, alpha-synuclein neuropathology was found in the ventromedial medulla (vmM) inhibitory neurons in the medullary reticular formation (RF). As shown in table 1 of that report, which listed the distribution of alpha-synuclein pathology and neuronal loss, the medullary RF had 2+ (moderate) Lewy bodies, 2+ Lewy neurites,

and 0 neuronal loss. Quantifying neuronal loss is far more important than identifying alpha-synucleinopathy pathology, since the presence of a protein deposit does not necessarily mean that this is the cause of clinical symptoms [1, 4]. Clearly, more postmortem histopathological studies of iRBD patients are needed.

40.3 Clinical-Neuropathological Study of PD and Probable RBD

PD patients in a longitudinal clinicopathologic study were screened for probable RBD with the Mayo Sleep Questionnaire [9]. After death, semiquantitative analyses were conducted for synuclein, amyloid, neurofibrillary tangles, and cerebrovascular lesions. Forty cases had probable RBD (PD+RBD) and 41 did not (PD-RBD). Despite similar age at death (∼80 years) and disease duration (∼14.5 years), PD+RBD patients had increased synuclein deposition in all brain regions examined, with 9 of 10 regions being significantly different. The Lewy body 10-region total score (scale = 0–40) was 29.5 in PD + RBD vs. 24.5 in PD-RBD patients, significantly different ($p = 0.002$).

40.4 Neuropathology of Prodromal Lewy Body Disease

A clinical-pathological case was reported of a 69-year-old man with iRBD who was assessed during a 10-year follow-up period with longitudinal clinical and laboratory tests [10]. He developed mild cognitive impairment, depression, hyposmia, and constipation. Parkinsonism was absent, but dopamine transporter imaging showed subclinical SN damage. Postmortem examination demonstrated neuronal loss and Lewy body pathology in the peripheral autonomic nervous system (e.g., cardiac and myenteric plexus), olfactory bulb, medulla, pons, SN pars compacta (estimated cell loss, 20–30%), nucleus basalis of Meynert, and amygdala. The neocortex was spared. This case illustrates how non-motor symptoms, along with widespread peripheral and central nervous system pathological changes, occur before parkinsonism onset and dementia onset in pathology-confirmed LBD. The authors pointed out that the current diagnostic criteria for PD do not detect these patients, who present only with non-motor symptoms.

40.5 RBD Is Related to Enteric Neuropathology in Idiopathic RBD and in RBD-PD

In one study, on α-synuclein immunoreactivity in iRBD, the expression of α-synuclein was investigated in colonic biopsies of patients with iRBD to address whether α-synuclein immunostaining of tissue obtained via colonic biopsies holds promise as a diagnostic biomarker for prodromal PD [11]. In a prospective study, patients with iRBD, patients with PD, and healthy controls underwent colonic

biopsies for comparison of α-synuclein immunoreactivity patterns between the groups by using two different antibodies. There was no difference in colonic mucosal and submucosal immunostaining between groups using the 15G7 α-synuclein antibody, which was found in almost all participants. In contrast, immunostaining for serine 129-phosphorylated α-synuclein (pSyn) in submucosal nerve fibers or ganglia was found in 4/17 iRBD patients, in 1/19 patients with PD, and 0/14 controls. The authors concluded that their findings of pSyn immunostaining of colonic biopsies in almost 25% of iRBD patients raised the possibility that this tissue marker may be a suitable candidate for further study as a prodromal PD marker in at-risk cohorts of iRBD patients.

The second study was designed to determine whether RBD in PD is associated with lesions and dysfunction of the autonomic nervous system by evaluating enteric phosphorylated α-synuclein histopathology (PASH) and permeability [12]. Forty-five patients with PD participated in a cross-sectional study. RBD was vPSG confirmed. Each patient had five biopsies taken at the junction between the sigmoid and descending colon during the course of a rectosigmoidoscopy. For the detection of enteric PASH, two colonic biopsies were analyzed by immunohistochemistry with antibodies against phosphorylated α-synuclein and PGP9.5 in 43 patients (2 patients were excluded because only one biopsy was available). In the three other biopsies mounted in Ussing chambers, the paracellular permeability and transcellular permeability were evaluated by measuring sulfonic acid and horseradish peroxidase flux, respectively.

The major finding was that enteric PASH was significantly more frequent in the subgroup of patients with PD + RBD compared to PD patients without RBD, 64.3% (18/28) vs. 13.3% (2/15) ($p < 0.01$). No differences were observed in intestinal permeability between patients with PD with and without RBD. Therefore, patients with PD + RBD have a greater frequency of synuclein pathology in the enteric nervous system, suggesting that RBD is associated with widespread synuclein neuropathology.

40.6 Skin Nerve Phosphorylated α-Synuclein Deposits in Idiopathic RBD

A study was conducted to determine whether phosphorylated α-synuclein (p-α-syn) deposits can be detected by means of skin biopsy in patients with iRBD, as a potential early histopathologic marker of impending overt clinical synucleinopathy [13]. Proximal (cervical) and distal (legs) samples of skin biopsy were obtained from 12 patients with vPSG-confirmed iRBD and 55 healthy controls (HC). P-α-syn deposits were assessed with a monoclonal antibody against p-α-syn at serine 129, disclosed by an immunofluorescence method. The patients also underwent an extensive workup to search for non-motor PD symptoms. P-α-syn deposits were detected in 75% (9/12) of patients with iRBD and in 0% (0/55) of the HC. In the iRBD patients, the sensitivity of the test was somewhat higher at the cervical site (67%) when compared to the leg site (58%). Therefore, from these preliminary findings, the authors suggested that skin biopsies in patients with iRBD might be a safe and sensitive

procedure to be further tested to detect of p-α-syn deposits in the premotor stage of synucleinopathies.

A second study [14] was prompted by the recent detection of phosphorylated alpha-synuclein (p-alpha-syn) deposits, one of the neuropathological hallmarks of PD, in dermal nerve fibers in PD patients with good specificity and sensitivity. Therefore, the investigators studied whether p-alpha-syn may serve as a biomarker in patients with a high risk of developing PD, such as those with iRBD. They compared the presence and distribution of p-alpha-syn deposits in dermal nerve fibers in 18 patients with iRBD, in 25 patients with early PD, and in 20 normal controls. Skin biopsy was taken at the level of C7 and Th10 and in the upper and lower leg. Presynaptic dopamine transporter imaging using FP-CIT-SPECT was performed in all patients with iRBD and in 11 patients with PD. All iRBD patients underwent olfactory function testing. The likelihood ratio (LR) for prodromal PD was calculated for each patient based on published research criteria. Skin serial sections were assessed by double-immunofluorescence labeling with antibodies to pSer129-alpha-syn under blinded conditions. P-alpha-syn was visualized in 10/18 patients with RBD (sensitivity of 55.6%) and in 20/25 early PD patients (sensitivity of 80%), but in none of the controls (specificity of 100%). The percentage of dermal structures innervated by p-alpha-syn-positive fibers was negatively correlated with dopamine transporter binding in the FP-CIT-SPECT ($\rho = -0.377$, $p = 0.048$), with olfactory function ($\rho = -0.668$, $p = 0.002$), and positively correlated with the total LR for iRBD to present prodromal PD ($\rho = 0.531$, $p = 0.023$). Dermal p-alpha-syn can therefore be considered a peripheral histopathological marker of synucleinopathy and can be detected in a subgroup of iRBD patients that presumably represents prodromal PD. Dermal p-alpha-syn is detectable in iRBD patients without PD motor symptoms and thereby stratifies this prodromal PD patient group, which may be relevant to future clinical trials testing disease-modifying agents.

40.7 Reduced Intraepidermal Nerve Fiber Density in Patients with Idiopathic RBD

Previous findings suggesting that certain cutaneous abnormalities, such as small fiber neuropathy and alpha-synuclein deposition, might reflect brain pathology, and thus might function as early biomarkers in PD, prompted a study to determine whether patients with iRBD already demonstrate any distinctive cutaneous features [15]. Skin punch biopsies from the distal leg were conducted on 18 iRBD patients and 22 controls using immunohistochemistry and microscopy. Further clinical evaluation included structured interviews, clinical motor and non-motor questionnaires and rating scales (e.g. Unified Parkinson's disease rating scale [UPDRS], non-motor symptoms questionnaire [NMS-Quest], Beck Depression Inventory, and Epworth Sleepiness Scale). There was also evaluation of cognitive and olfactory functioning as well as blood samples.

The major finding was that intraepidermal nerve fiber density (IEFND) was reduced in iRBD patients compared to controls ($p = 0.037$), whereas the axon

swelling ratio did not differ between groups. Patients with iRBD reported PD non-motor symptoms more frequently than controls (UPDRS I, NMS-Quest). Olfaction and daytime sleepiness differed between both groups, whereas there were no differences regarding cognition. These *in vivo* findings demonstrated small fiber neuropathy in iRBD patients that are associated with PD non-motor symptoms, thus indicating that peripheral abnormalities may occur early in iRBD. The prognostic value of these findings needs to be investigated in longitudinal studies.

40.8 Assessment of α-Synuclein in Submandibular Glands in Patients with Idiopathic RBD

The rationale for this study was that in patients with PD, deposits of intraneuronal aggregates of phosphorylated αSyn are found in the autonomic nerve fibers of the submandibular gland. And so since patients with iRBD often develop PD and other synucleinopathies, an investigation was conducted to determine whether αSyn deposits could also be detected in the submandibular gland nerve fibers of iRBD patients [16]. Findings from a case-control study were reported with the method involving a transcutaneous core needle biopsy of the submandibular gland in patients with PSG-confirmed iRBD, patients with PD, and controls. The presence of αSyn was assessed with immunohistochemistry using 129-phosphorylated antiserine monoclonal antibody. Submandibular biopsy material containing glandular parenchyma was obtained in 9/21 patients with iRBD, 12/24 patients with PD, and 26/26 controls. αSyn aggregates were detected in nerve fibers of the glandular parenchyma in 8/9 (89%) iRBD patients, in 8/12 (67%) of PD patients, and in 0/26 (0%) of controls. In the patients whose biopsy samples did not contain glandular parenchyma, deposits of αSyn were found in extraglandular tissues in an additional 3/12 iRBD patients and in an additional 5/12 PD patients. None of the controls showed αSyn immunoreactivity in extraglandular tissues. There were minimal side effects from the procedure. Therefore, in patients with iRBD, submandibular gland biopsy is a safe procedure for the detection of αSyn aggregates. Also, this form of αSyn detection could be useful for histological confirmation in individuals with clinically diagnosed PD.

40.9 α-Synuclein Aggregates in Labial Salivary Glands of Patients with Idiopathic RBD

A prospective study had the purpose of assessing whether biopsies of the labial minor salivary glands could detect, in a safe manner, phosphorylated α-synuclein (pAS) deposits in patients with idiopathic RBD (iRBD) [17], given how iRBD is known to precede the overt manifestations of α-synuclein neurodegenerative disorders, mainly Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Labial biopsies of the minor salivary glands were performed in 62 iRBD patients, 13 PD patients, 10 DLB patients, and 33 controls. (The PD and DLB patients had

originally been diagnosed with iRBD before converting to overt neurodegeneration.) Aggregates of pAS were assessed by immunohistochemistry using antiserine 129-phosphorylated α-synuclein antibody and the conformation-specific 5G4 antibody. Sufficient biopsy material containing glandular parenchyma was obtained in all participants. Deposits of pAS were found in 50% (31/62) of iRBD patients, in 54% (7/13) of PD patients, in 50% (5/10) of DLB patients, and in 3% (1/33) of controls. Patients with iRBD, PD, and DLB, with or without pAS immunoreactivity, did not differ in any demographic or clinical features. Adverse events included lip bruising (9.2%), lip swelling (6.6%), pain (2.4%), and numbness (1.7%), which were mild and transitory and did not require intervention. Therefore, labial minor salivary gland biopsy proved to be a safe and useful procedure to identify pAS in patients with iRBD, and also in PD and DLB patients initially diagnosed with iRBD. The biopsy findings provided direct histopathological evidence that iRBD represents an α-synucleinopathy.

40.10 Predicting α-Synuclein Pathology by Probable RBD Diagnosis

A prospective study had the aim of determining the predictive value for postmortem histopathology-confirmed α-synucleinopathy in a cohort of patients with "probable RBD" (pRBD) diagnosed by the Mayo Sleep Questionnaire (MSQ) [18]. From 2007 to 2018, 602 subjects in the Arizona Study of Aging and Neurodegenerative Disorders had clinician assessments for pPRBD (including 298 subjects with MSQ support and 304 subjects without MSQ completion), underwent serial cognitive and motor examinations, and ultimately had postmortem neuropathological examinations. Mean age at death was 85 years. Histological evidence of α-synuclein pathology was found in 79% (80/101) of cases with pRBD and in 39% (198/501) of cases without pPRBD ($p < 0.001$). Overall sensitivity for predicting an α-synucleinopathy by pRBD diagnosis was 29%, specificity was 93%, positive predictive value was 79%, and negative predictive value (NPV) was 60%. Diagnosis of pPRBD was less frequently present in subjects without α-synuclein pathology. pRBD was not present in any of 46 subjects with incidental Lewy body disease (ILBD). Therefore, the MSQ-supported diagnosis of pPRBD appears useful for predicting α-synucleinopathy in manifest neurodegenerative disease, but not necessarily in ILBD. Additional prospective autopsy research is needed in this area, with the inclusion of patients with polysomnography-confirmed RBD (as "prodromal parkinsonism") being critical.

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Genetics of REM Sleep Behavior Disorder

41

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41.1 The Importance of Studying the Genetics of REM Sleep Behavior Disorder

Evidence from long-term prospective cohorts suggest that given enough follow-up time, more than 90% [1], and possibly 100%, of true video-polysomnography (vPSG) documented REM sleep behavior disorder (RBD) patients will progress to an overt synucleinopathy, either Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA) [2–5]. Most research on PD, DLB, and MSA is focused on at least one of the following three main research aims: (1) identifying the underlying pathogenic mechanisms, (2) developing a cure or symptomatic treatment, and (3) early diagnosis and management. Genetic studies of these diseases can assist in reaching all these three aims. Since genetic studies on PD, DLB, and MSA are already being performed routinely, what would be the added value of specifically studying RBD genetics? To better understand the answers to this question, one should consider the following: (a) PD and DLB probably represent an umbrella for several disease subtypes [6, 7], with similar general phenotypes but with different underlying genetic and biological mechanisms, ages at onset, rates of progression, different additional symptoms, etc; (b) Individuals with RBD who develop PD often represent a specific subtype of PD, with typical clinical features [8]; (c) The progression to PD, DLB, or MSA from RBD is variable, ranging from immediate to decades after the onset of RBD [1, 4, 9, 10], and it is not clear which factors determine the rate and type of progression.

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Genetic studies of RBD can address all these research aims and issues and further advance our understanding of all three synucleinopathies. Since genetic studies of PD include all the different PD subtypes, it is likely that there are novel genetic factors that are associated specifically with the RBD subtype, which are diluted in the genetic data of all PD patients and therefore remain unidentified. Furthermore, studying RBD may identify genetic factors that are associated with the age at onset of RBD and the subsequent synucleinopathies, with the rate of progression, and with the type of the resulting synucleinopathy. Such genetic factors will be valuable for prognosis and for planning of treatment. In the conclusion of this chapter, we will discuss how genetic studies of RBD should be performed in order to reach these goals.

41.2 Genetics of RBD-Associated Synucleinopathies: An Overview

Since RBD may convert to either PD, DLB, or MSA, it is likely that at least partial genetic overlap between these disorders and RBD exists. Most of the genetic studies on RBD conducted thus far aimed to examine this possible overlap; thus, we will briefly summarize the genetic background of PD, DLB, and MSA. Figure 41.1 details the genes implicated in these diseases according to the level of confidence in the genetic association.

41.2.1 Parkinson's Disease

Until 1997, when the first mutations directly linked to Parkinson's disease (PD) were described in the *SNCA* gene [11], PD was considered as a purely sporadic, nongenetic disorder, mainly due to the lack of concordance in twin studies [12, 13]. However, current estimations of the portion of PD attributed to genetic factors may range between 27% in population-based studies [14, 15] and 60% in familial studies [16]. Thus far, more than 40 genetic loci and genes are known or suspected to be involved in PD and parkinsonism [17–19]. These include variants that are associated with mildly increased or decreased risk for PD, variants that are strong risk factors for PD, mutations that cause PD in autosomal dominant or recessive manner, and mutations that cause atypical forms of parkinsonism (Fig. 41.1).

The genes that harbor mutations most commonly associated with PD are *GBA* [20, 21] and *LRRK2*. Mutations in these genes have variable effects on risk for PD, and their combined frequency is 3–20% of patients in most populations and up to 30–40% in Arab-Berbers and Ashkenazi Jews [20–27]. *GBA* mutations can be classified as severe or mild, based on their resulting phenotype in Gaucher's disease (GD). Severe *GBA* mutations are those that when inherited from both parents lead to the severe types of GD (types 2 and 3), while mild mutations are those that lead to the milder form of GD, type 1. Carriers of severe *GBA* mutations are at higher risk for PD as compared to mild mutation carriers and present with motor symptoms

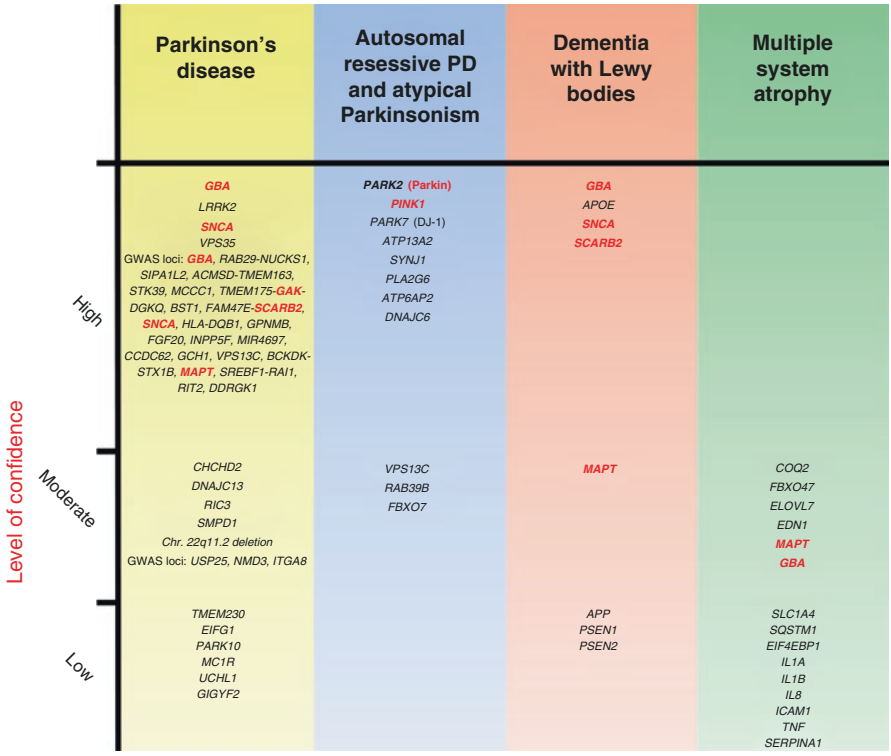

Fig. 41.1 Genes implicated in Parkinson's disease, atypical Parkinsonism, dementia with Lewy bodies, and multiple system atrophy. Genes implicated in Parkinson's disease, atypical Parkinsonism, dementia with Lewy bodies, and multiple system atrophy are organized according to the level of confidence in their involvement in these diseases. These genes were identified in case-control studies, with candidate gene approach, genome-wide association studies, and family-based studies. Genes in red are those that may have a role in REM sleep behavior disorder; however, note that the role of many of the other genes in RBD has not been studied yet

at an earlier age [20]. *GBA*-associated PD is more common in men, similar to the increased male/female ratio seen in sporadic PD [22]. Different *LRRK2* mutations also have variable effects on the risk for PD [28]; the p.G2019S and the p.R1441C/G/H substitutions are associated with high risk for PD [25, 29], while the p.G2385R substitution, common among Asians, is associated with a smaller increase in risk for PD [23, 28]. In contrast to *GBA*-associated PD and idiopathic PD, the male/female ratio in *LRRK2*-associated PD is 1:1 [23].

Less than 2% of all PD cases can be attributed to mutations in other genes [17, 19]. The first mutations that lead to autosomal dominant PD were described in the *SNCA* gene [11], encoding α-synuclein, the protein which accumulates in Lewy bodies. Triplications, duplications, and point mutations in *SNCA* were reported in early-onset, autosomal dominant PD [30]. Rare mutations in *VPS35* are the only other well-validated cause for autosomal dominant, typical PD. These mutations

probably account for less than 0.5% of PD patients [31–33]. There is some evidence that mutations in other genes, including *CHCHD2* [34], *DNAJC13* [35], *TMEM230* [36], and *RIC3* [37], may also cause autosomal dominant PD. However, evidence for most of these genes is still controversial, and in the case of *DNAJC13* and *TMEM230*, since both genes were implicated using the same large family [35, 36], at least one of them is probably not a PD-associated gene. Lastly, carriage of several heterozygous *SMPD1* mutations may strongly increase the risk for PD [38–40]. However, additional research is required to determine whether mutations in these genes indeed cause PD.

Homozygous and compound heterozygous mutations in *PARK2* (Parkin) are the most common cause of autosomal recessive PD, accounting for 8.6% of PD with age at onset younger than 50 years [41]. Mutations in *PINK1* and *PARK7* (DJ1) are other well-validated causes of autosomal recessive, early-onset PD [41]. Heterozygous mutations in these genes (*PARK2* [42], *PINK1* [43], and *PARK7* [44]) may also be risk factors for typical, late-onset, or early-onset PD, but more studies are needed to confirm these possible associations. Other genes that are often cited as autosomal recessive PD-causing genes in fact lead to atypical forms of parkinsonism, and their role in typical PD is still not clear.

The largest genome-wide association study (GWAS) of PD performed to date identified 28 markers in 24 loci which were associated with increased or decreased risk for PD [18]. These loci include a few known PD-related genes such as *GBA*, *LRRK2*, *SNCA*, and possibly *GCH1* [45] but mostly genes that were not previously associated with PD. *VPS13C* mutations, one of the genes implicated in the GWAS, were identified in severe, rapidly progressive autosomal recessive parkinsonism [46]. It is important to note that although the calculated effects on PD risk associated with these GWAS markers are small, with odds ratios (OR) typically ranging between 0.75 and 1.80 [18], each loci can harbor genetic variants with either minor, medium, or major effect of the risk for PD.

41.2.2 Dementia with Lewy Bodies

About one out of five dementia cases is due to DLB, making it the second most common dementia after Alzheimer's disease [47]. Despite being relatively common, the genetic background underlying DLB is mostly still unknown. Interestingly, the available data suggest that DLB shares some genetic risk factors with PD (e.g., *GBA* variants) and shares other genetic risk factors with Alzheimer's disease (AD, e.g., the *APOE* e4 allele) to which it is more genetically similar [48]. As with PD, one of the most common genetic risk factors for DLB is *GBA* mutations that may be found in up to one third of DLB patients in some populations [49, 50]. In a multicenter study that included 721 DLB patients and 1962 controls from 11 centers worldwide, the odds ratio to have a *GBA* mutation was 8.28 [49], which is higher than the risk estimates of *GBA* mutations for Parkinson's disease [21]. Recently, it was demonstrated that a rare *MAPT* haplotype, H1G, with an allele frequency of about 0.01 in the general population, is associated with a threefold risk for DLB

[51]. An association study of 54 genomic regions in a cohort of 788 DLB cases (including 667 pathologically confirmed) identified variants in the *APOE*, *SCARB2*, and *SNCA* loci associated with risk for DLB [52]. The *APOE* e4 allele is the most common risk factor for AD [53], and it is also a risk factor for DLB [54]. The *SCARB2* and *SNCA* loci are both strongly implicated in PD [18], further demonstrating that DLB has a genetic overlap with both AD and PD. This may suggest that despite having a similar clinical presentation, DLB can be subdivided into different subgroups based on their genetic background. Furthermore, genes that are associated with familial forms of AD, such as *APP*, *PSEN1*, and *PSEN2*, may be associated with Lewy body pathology typical to DLB [55–57].

41.2.3 Multiple System Atrophy

MSA, being a less common disease than PD and DLB, with an estimated incidence of 3–4/100,000 of individuals older than 50 years, has a genetic basis that is still poorly understood. There are no genetic factors that have been unequivocally demonstrated to cause or to be associated with MSA. A recent GWAS including 918 MSA patients and 3864 controls did not identify genetic markers with genome-wide significance but reported variants in the *FBXO47*, *ELOVL7*, *EDN1*, and *MAPT* genes as potentials for follow-up studies [58]. A previous study has already suggested an association between *MAPT* and MSA [59], although an older study did not identify this association [60].

Other studies specifically examined PD-related genes in MSA. An association between *SNCA* locus variants and risk for MSA has been reported in three studies, perhaps specifically associated with the cerebellar type of MSA [61–63], but this association was not confirmed in the recent GWAS [58]. Mutations in *GBA*, strongly implicated in both PD and DLB, have been studied in MSA as well, with conflicting results. The largest study performed thus far, including 969 MSA patients and 1509 controls, suggested that *GBA* mutations are indeed associated with MSA as well, more strongly with the cerebellar type [64]. However, the risk (OR of 2.4) was much smaller of that observed in PD or DLB [20, 49], and additional studies, although smaller, did not identify an association between *GBA* mutations and MSA [65–67]. Finally, while pathogenic *LRRK2* mutations that cause PD are not associated with MSA [68, 69], it was demonstrated that a specific *LRRK2* haplotype may be associated with a reduced risk form MSA [70], yet this finding also awaits further replication.

A study of a consanguineous family with MSA demonstrated that homozygous variants in the *COQ2* gene segregated with the disease, and these variants were more common in the heterozygous state in additional MSA patients compared to controls [71]. However, subsequent studies did not replicate this association [72–75], and a recent GWAS did not identify an association around the *COQ2* locus [58].

Several candidate gene studies have been performed in order to examine potential association to genes involved in oxidative stress and immune response, since these mechanisms are implicated in the pathogenesis of MSA. Associations with

MSA were reported for variants in *SLC1A4*, *SQSTM1*, *EIF4EBP1* [76], *IL1A* [77], *IL1B* [78], *IL8*, *ICAM1* [79], *TNF* [80], and *SERPINA1* (alpha-1-antichymotrypsin gene) [81]. However, these were all reported in single studies and were not replicated, and none of these loci was implicated in the MSA GWAS [58].

Isolated cases of MSA, whether pathologically confirmed or not, were reported to be associated with cerebellar ataxia genes and the *C9orf72* gene, but there is no further evidence for the association of these genes with MSA [82].

41.3 Genetic Studies of RBD

The association between synucleinopathies and RBD was initially reported more than two decades ago, yet only recently have the first genetic studies focusing on RBD been performed. Thus far, the strongest genetic factor associated with RBD is *GBA* mutations [83]. Clinically, *GBA*-associated PD and RBD-associated PD share several motor and non-motor features. Both are associated with faster motor progression [8, 84] and the postural-instability-gait-dysfunction phenotype [22, 85, 86]. In terms of non-motor symptoms, the most striking similarity is in the rate and progression of cognitive decline and progression to dementia [84, 87–90]. Therefore, the role of *GBA* mutations in RBD was among the first to be studied in a cohort of idiopathic RBD patients, demonstrating a strong association with an odds ratio of 6.24 for carriers of *GBA* mutations [83]. This association may be stronger than the association of *GBA* mutations with PD in a similar population [91] and comparable to the association of *GBA* mutations with DLB. This association was confirmed in an additional study of 171 RBD patients from the UK [92]. This may suggest that mutations in *GBA* are more specifically associated with the RBD subtype of PD. Further supporting this observation, *GBA* mutations were associated with probable RBD in a cohort of PD patients screened with an RBD questionnaire [83]. Interestingly, among carriers of biallelic *GBA* mutation and among heterozygous carriers who did not have PD, scores in the RBD questionnaires were significantly worse than for controls and worsened more over a follow-up of 2 years [93]. In addition, it is possible that in both RBD- and *GBA*-associated PD, there is a more diffuse spread of α-synuclein [94, 95].

Unlike PD associated with *GBA* mutations, patients with *LRRK2*-associated PD seem to have a more benign disease course, with less rapid cognitive decline [96], less hyposmia, and less autonomic dysfunction compared to sporadic PD [97]. Accordingly, thus far mutations in *LRRK2* are not implicated in idiopathic RBD [92, 98] nor in PD patients with probable RBD based on questionnaires [99]. Furthermore, there was a reduced occurrence of RBD among carriers of *LRRK2* mutations in two cohorts of PD patients [100, 101]. Additional support for the lack of association between *LRRK2* mutations and RBD is provided by the different male/female ratios in *LRRK2*-associated PD (1:1) [23] and RBD (2:1–8:1) [10, 102].

To examine the role of known PD GWAS loci, one study genotyped nine SNPs from loci that were previously associated with PD. The *SCARB2* and *MAPT* loci were associated with risk for RBD, and a marginal association was found at the

GAK and *SNCA* loci [103]. Subsequently, another study in a smaller population which examined other SNPs at the *SNCA* and *MAPT* loci also identified an association with *MAPT*, but not with *SNCA* [104]. However, the latter study was underpowered and examined only one SNP at the *SNCA* locus; therefore, it is likely that other *SNCA* variants may be associated with RBD. A small study in 56 patients with RBD and 57 patients with PD suggested that variants in the 3′ of *SNCA* were more frequent in PD than in RBD [105]. *SCARB2* encodes a transporter responsible for transferring the enzyme encoded by *GBA*, glucocerebrosidase, from the endoplasmic reticulum to the lysosome [106]. Therefore, this finding may provide additional support for the important role of *GBA* in RBD. However, larger studies are necessary to determine if RBD is associated with other known PD loci and if patients with RBD have a unique genetic background that can distinguish them from other subtypes of PD/DLB.

Due to the association of hexanucleotide repeat expansions in C9orf72 with frontotemporal dementia and amyotrophic lateral sclerosis and their potential (albeit weak) association with PD [107] and MSA [108], a small study examined their role in RBD. Two RBD patients with C9orf72 expansion were identified [109]. However, to examine whether this was a random finding or a valid association, a much larger study is needed. Another gene with possible yet controversial involvement in PD, *MC1R* [110–113], was found to not be involved in RBD [114].

The *APOE* ε4 allele is probably the most important genetic risk factor for Alzheimer's disease and DLB. However, a recent study demonstrated that the *APOE* ε4 allele is not associated with an increased risk for RBD nor for conversion from RBD to an overt synucleinopathy [115].

There is some evidence suggesting that genetic factors may be associated with the progression rate from RBD to PD, DLB, or MSA [103]. However, this hypothesis must be studied in larger cohorts, since it is based on a very small number of RBD patients studied. If this hypothesis can be further established and genetic factors are indeed associated with RBD progression rate, it may be possible to prioritize RBD patients for clinical trials not only based on their clinical data but also based on their genetic background.

41.4 RBD in Familial Forms of Parkinson's Disease

Other genetic forms of PD, which are not caused by *GBA* or *LRRK2* mutations, are rare and probably account for less than 2% of all PD patients [17]. Furthermore, in many of the clinical studies describing families with a genetic form of PD, RBD was not tested using PSG or only partially assessed using clinical history. Therefore, the information on RBD in familial forms of PD is limited, and Table 41.1 summarizes the current knowledge on RBD in patients with mutations in the genes implicated in familial PD.

In patients with *SNCA* single amino acid mutations, duplications, or triplications, RBD was described, but it is not clear if it is more, or less, common than in sporadic, nongenetic PD. In a study that included 11 patients with *SNCA* gene duplication,

Table 41.1 Important familial and sporadic Parkinson's disease genes and REM sleep behavior disorder

Gene	Involvement in PD	Involvement in RBD	Comments
GBA	One of the two most common genetic risk factors for PD	Strongly associated with RBD	The association with RBD seems to be stronger than with PD
LRRK2	One of the two most common genetic risk factors for PD	Pathogenic mutations are not associated with RBD	Full sequencing is required to determine role of other *LRRK2* variants in RBD
SNCA	Point mutations, duplications, and triplications lead to sporadic PD; common variants are associated with risk for PD	Only a few *SNCA* genetic markers were analyzed, showing weak or no association with RBD risk	Copy number variations as well as point mutations and other PD- or DLB-associated markers need to be studied
PARK2	Biallelic mutations cause autosomal recessive, early-onset PD	Contradicting evidence on frequency of RBD in patients with *PARK2*-associated PD	Copy number variations and full sequencing studies are needed to determine the role of *PARK2* in RBD
PINK1	Biallelic mutations cause autosomal recessive, early-onset PD	Limited evidence for involvement of *PINK1* in RBD	Heterozygous mutations in *PINK1* may be a risk factor for RBD, yet additional studies are needed to determine the role of *PINK1* in RBD
PARK7	Biallelic mutations cause autosomal recessive, early-onset PD	No studies were performed on *PARK7* in RBD, and RBD was not reported in individuals with *PARK7*-associated PD	Full sequencing studies of *PARK7* are needed to determine its role in RBD
MAPT	Common haplotypes are associated with risk for PD	Some evidence suggest that the PD-associated haplotypes may be involved in RBD	Larger studies that include sub-haplotypes of *MAPT* are needed to determine its role in RBD
SCARB2	Encoding the transporter of *GBA*, common SNPs are associated with PD	One study demonstrated an association between one *SCARB2* SNP and RBD	Larger studies with additional markers are needed to determine the role of *SCRAB2* in RBD
VPS35	Rare *VPS35* variants cause autosomal dominant PD	No studies were performed on *VPS35* in RBD, and RBD was not reported in PD patients with *VPS35* mutations	Full sequencing studies of *VPS35* are needed to determine its role in RBD

RBD was reported in three patients, was not reported in five, and was not assessed at all in three patients [116]. In another study that performed PSG on four carriers of the *SNCA* p.E46K mutation, no REM sleep was documented in three of them [117], thus not allowing to determine whether RBD exists in these patients. Other studies mostly provided data based on clinical history and patient self-report [118];

therefore, additional studies on *SNCA*-associated PD patients are needed to determine whether RBD is more frequent among them.

There are conflicting data on RBD occurrence in patients with autosomal recessive PD due to *PARK2* (Parkin) mutations. A video-PSG study of ten patients with *PARK2* mutations confirmed RBD in six of them, but in all cases RBD followed the onset of the motor symptoms and was characterized mainly by jerks [119]. In another study of 11 patients, 5 (45%) had REM sleep without atonia, but only 1 (9%) had definite RBD [120], and an additional study did not identify RBD in any of the 6 patients who were tested with PSG [121]. Lack of RBD would be in accordance with the lack of Lewy bodies frequently observed in *PARK2*-associated PD, and so additional studies are needed.

In PD patients with homozygous or compound heterozygous mutations in *PINK1*, there is only little information on RBD. In three siblings with homozygous *PINK1* mutations, PSG studies did not identify RBD [122]. Interestingly, a patient with heterozygous *PINK1* and heterozygous *PARK2* mutations was reported to have RBD [123], but it was not confirmed by PSG and could be coincidental. Recently, it was suggested that a heterozygous *PINK1* variant, p.G411S, is associated with an increased risk for PD [124], and two RBD patients with this variant were identified [125]. However, the overall effect of this variant is comparable to those found in GWAS (i.e., small effect size), and so it may only have a minor role in PD and RBD susceptibility.

Currently, there are no data on the occurrence of RBD in other familial forms of PD or parkinsonism associated with genes such as *PARK7*, *VPS35*, *SMPD1*, *ATP13A2*, and others.

41.5 The Overlap Between the Genetics of RBD, PD, and DLB

Although the genetic data on RBD are still limited, it is already clear that there is only a partial overlap of RBD genetic background with PD, DLB, and MSA genetics, suggesting that RBD may represent a clinical subtype with its own specific genetic background. While *GBA* mutations are associated with RBD, PD, DLB, and potentially MSA, *LRRK2* mutations are PD specific (and therefore may represent a specific subtype of PD) and that the *APOE* ε4 allele is specific to DLB. This haplotype may also represent a specific DLB subtype, perhaps those that present with more tau pathology and not only synucleinopathy. Further deciphering the commonalities and differences in the genetic backgrounds of all these conditions will allow a better identification of the different subtypes of patients that are gathered under the umbrellas or PD and DLB, toward the goal of precision medicine.

It is important to consider that some of the genetic markers identified in PD GWASs may be specific to RBD-associated PD and that these markers may demonstrate a significant association with PD due to the high occurrence of RBD in PD cohorts compared to controls. Therefore, the power of PD GWASs and its ability to identify novel genetic associations in PD could be increased by specifically selecting PD patients with RBD (or patients with other markers of disease subtypes). The same applies for DLB, despite the fact that large GWASs of DLB are still not available.

41.6 Conclusions and Future Aspects

Understanding the genetic background of RBD and its progression to the different synucleinopathies may be of great importance toward future prognosis, genetic counseling, patient stratification for clinical trials, and precision medicine. To properly map the genetic risk loci in RBD, two approaches could be taken: (1) performing GWAS on idiopathic, objectively vPSG documented, and properly phenotyped RBD cohorts and (2) reanalyzing data from the PD GWASs only for PD patients who also have RBD or patients who had RBD prior to the development of overt PD. Once DLB GWASs are also available, a similar approach could be taken.

Once genetic factors that affect either the rate of progression from RBD to synucleinopathies or to the specific type of synucleinopathy (i.e., genetic markers that predict conversion to either PD, DLB, or MSA specifically), better prognosis and genetic counseling could be given. The idea of providing genetic counseling to individuals who still have not developed an overt synucleinopathy is still controversial, but it is likely that once specific treatments for specific genetic subtypes of PD, DLB, or MSA are available, such counseling will be necessary. Some argue that even today, carriers of specific mutations that cause or significantly increase the risk for PD should receive genetic counseling, to properly prepare for the future.

Currently, there are no clinical trials performed on RBD patients in order to prevent or slow down the progression to an overt synucleinopathy. One of the reasons for this is practical, since it is difficult to determine which RBD patients will progress rapidly, as the average time from diagnosis of RBD to development of PD, DLB, or MSA may be more than a decade. Since clinical trials cannot extend for such a long period, it will be crucial to stratify RBD patients and identify those who are likely to progress most rapidly. One way to stratify these patients is by using other clinical measures, such as motor, smell, and color discrimination tests [9]. Adding genetic factors that are associated with the rate of progression is likely to improve the stratification and better identify RBD patients who will progress rapidly to an overt synucleinopathy and thus become more preferred disease-modifying study patients.

Lastly, there are already drugs in development and in clinical trials that target a specific gene or its protein product, such as *GBA*, *LRRK2*, and *SNCA*. Therefore, identifying RBD patients with variants of these genes, as well as the identification of novel genes that may be associated specifically with RBD, may bring us one step closer toward precision medicine, tailored for each patient based on his or her genetic background and biological process responsible for the disease.

Note Added in Proof: Additional RBD—genetics papers have been published/accepted between the revision of this chapter and the proof: 1. Gan-Or Z, Alcalay RN, Rouleau GA, Postuma RB. Sleep disorders and Parkinson disease; lessons from genetics. Sleep Med Rev. 2018. https://doi.org/10.1016/j.smrv.2018.01.006. 2. Bjørnarå KA, Pihlstrøm L, Dietrichs E, Toft M. Risk variants of the α-synuclein locus and REM sleep behavior disorder in Parkinson's disease: a genetic association study. BMC Neurol. 2018. https://doi.org/10.1186/s12883-018-1023-6. 3. Toffoli M, Dreussi E, Cecchin E, et al. SNCA 3'UTR genetic variants in patients with Parkinson's disease and REM sleep behavior disorder. Neurol Sci. 2017. https://doi.org/10.1007/s10072-017-2945-2. 4. Fernandez-Santiago R, Iranzo A, et al. MAPT association with REM sleep behavior disorder. Neurol Genet.

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This paper adds 17 new loci associated with risk for Parkinson's disease and should be considered with in Fig. 41.1 and Sect. 41.2.1. 1. Li J, Ruskey JA, Arnulf I, et al. Full sequencing and haplotype analysis of MAPT in Parkinson disease and REM sleep behavior disorder. Mov Disord. In press.

This paper examined large PD, DLB and RBD cohort and demonstrated that MAPT variants and haplotypes are not associated with RBD.

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Animal Models of REM Sleep Behavior Disorder

42

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42.1 Introduction

REM sleep behavior disorder (RBD) is characterized by dream-enacting motor behaviors during REM sleep, which is normally quiescent with a display of brief myoclonic twitches amid prevailing muscle paralysis throughout the body. The majority of older adult RBD patients in one series experienced episodes of punching (87%), kicking (82%), falling out of bed (77%), gesturing (73%), or knocking over the nightstand (67%) during vivid dreams. Nearly all patients also reported vocalizations, most commonly talking (96%), screaming (90%), and moaning (64%). In both men and women, about 60% of patients and 20% of bed partners had sustained injuries [1]. Long before RBD was formally described as a parasomnia in humans in 1986 [2], the polygraphic hallmark of this disease, REM sleep without atonia, had been extensively studied in animals. These studies were pioneered by Michel Jouvet, who first identified the physiological features including muscle atonia during REM sleep (or "paradoxical sleep" as coined by Jouvet) in the cat in 1959 and described the "oneiric" or hallucinatory behaviors during REM sleep in those cats that recovered from bilateral electrolytic lesions of the dorsolateral pontine tegmentum, which included locus coeruleus and adjacent areas [3]. The abnormal behaviors during REM sleep in the cat elicited by lesions in pontine tegmentum range from simple

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movements such as body jerks to more complex, coordinated behaviors of hissing, piloerection, pouncing, attacking non-existing prey, walking, and running.

42.2 Brainstem Circuitry for REM Sleep Atonia

The level of tonic activity in skeletal muscles, except for the diaphragm and extraocular muscles, is low in NREM sleep and minimal in REM sleep. Cranial and spinal motor nuclei receive extensive projections from the caudal brainstem, the medulla and the pons (Fig. 42.1). Magoun and Rhines [4] first showed that the medial and lateral portion of the medulla has inhibitory and excitatory effects on motor activity, respectively. Electrical stimulation of the medial medulla inhibits both phasic and tonic motor activities such as flexor patellar and blink reflexes, motor responses induced by stimulation of the motor cortex, and muscle tone in the decerebrate animal. On the other hand, stimulation of the lateral medulla increases the patellar reflex [4]. The medullary inhibitory area in the cat includes the nucleus gigantocellularis (NGC) in the dorsal and the nucleus magnocellularis (NMC; nucleus gigantocellularis alpha in the rodents) in the ventral rostral medial medulla, as well as the nucleus

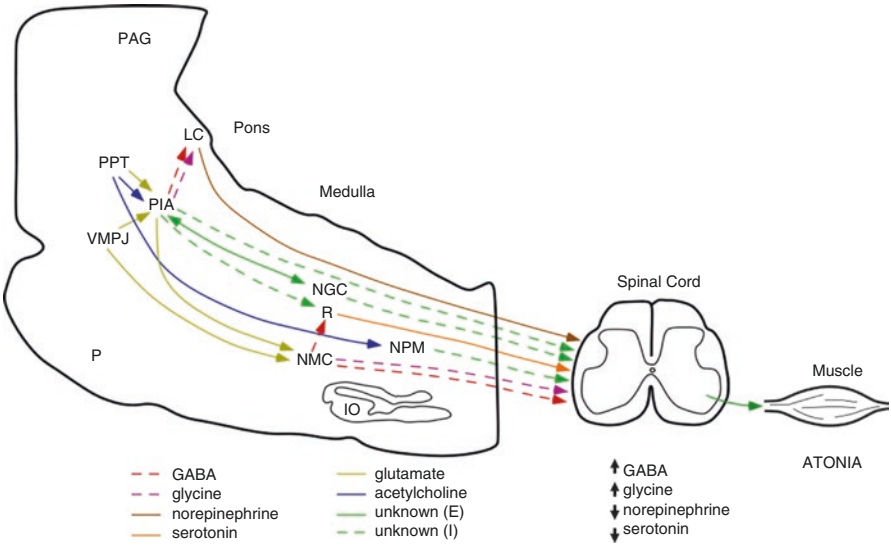

Fig. 42.1 A hypothetical neural circuit and transmitters involved in the control of REM sleep atonia. Solid and dashed lines represent excitatory and inhibitory effects on the target site. Glutamatergic and cholinergic activation of the pontine inhibitory area (PIA) elicits muscle atonia, which results from a combination of activation of GABAergic and glycinergic neurons in the nucleus magnocellularis (NMC) of the rostral ventromedial medulla and inactivation of noradrenergic neurons in the pontine locus coeruleus and medullary raphe serotonergic neurons. The pontine glutamatergic and cholinergic innervations originate from the ventral mesopontine junction (VMPJ) and pedunculopontine nucleus (PPT). Neurons in the VMPJ and PPT also project to the NMC, as well as to the nucleus paramedianus (NPM) of the caudal medial medulla. *IO* inferior olivary nucleus, *LC* locus coeruleus, *NGC* nucleus gigantocellularis, *P* pyramidal tract, *PAG* periaqueductal gray, *R* medullary raphe nucleus, unknown (E) and unknown (I): transmitter that exerts excitatory and inhibitory effect on the target site

paramedianus (NPM) in the caudal medial medulla. The motor inhibitory area is not limited to the medial medulla but extends to the medial pons and the ventral midbrain [5]. Muscle tone is decreased with electrical stimulation of the medial pons (the pontine inhibitory area (PIA)), the rostral ventral paralemniscal field of the pons, the pedunculopontine nucleus (PPT), the retrorubral nucleus, or the substantia nigra [5].

Anatomically, the NMC receives glutamatergic projections from the PIA (Fig. 42.1), the ventral paralemniscal tegmental field, the retrorubral nucleus, and the caudal ventral mesencephalic reticular formation [6]. The NPM receives cholinergic projections from the PPT and dorsolateral tegmental nucleus [7]. Three distinct areas, the glutamatergic-receptive NMC, the cholinergic-receptive NPM, and the glutamatergic-/cholinergic-insensitive NGC, can be identified by their motor response to chemical injections into the medial medulla (Fig. 42.2). Injection of non-NMDA receptor agonists, AMPA, and kainic acid into the NMC or injection of acetylcholine into the NPM elicits muscle atonia in decerebrate animals [8, 9]. These effects can be reversed by their antagonists, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 6-cyano-7-dinitroquinoxaline-2,3-dione (DNQX) injected into the NMC or atropine injected into the NPM [9, 10]. The induced suppression of muscle tone by chemical injection has also been observed in the behaving animal.

Glutamate injected into the NMC or acetylcholine injected into the NPM in wakefulness decreases muscle tone and suppresses eye movement without changing EEG activity in the chronic cat [10], suggesting that neuronal activity of the NMC and NPM is involved in the control of eye movement and motor activity, but not the EEG activity in sleep. Furthermore, the suppression of eye movement and muscle tone, resembling NREM sleep, by activation of NMC or NPM, indicates that neurons of the medial medulla may start to increase firing in NREM sleep resulting in a quiescent state of motor activity. The increased medial medullary neuronal activity continues and reaches its maximum in REM sleep. REM-on neurons have been recorded in the NMC and NPM [11]. In addition to the inhibition of tonic motor activity, the NMC may also be involved in the control of phasic motor activity. Microinjection of an NMDA agonist into the NMC elicits phasic motor events including rhythmic locomotor-like activity in the decerebrate animals, and this effect can be attenuated by D,L-2-amino-5-phosphonovaleric acid (APV) [8, 9].

The PIA receives cholinergic projections from the PPT and glutamatergic projections from the retrorubral nucleus and the PPT (Fig. 42.1) [12]. In contrast to the medial medulla, which can only be activated by either glutamatergic (NMC) or cholinergic (NPM) agonist, the PIA can be activated by both glutamatergic and cholinergic agonists (Fig. 42.2). AMPA or kainic acid injected to the PIA generates muscle atonia, whereas NMDA injected into it increases muscle tone. The pontine inhibitory and excitatory effects on motor activity can be blocked by CNQX/DNQX and APV, respectively [8]. Injection of cholinergic agonists, carbachol and acetylcholine, into the PIA elicits muscle atonia in decerebrate animals [8, 9]. However, muscle atonia induced by activation of the PIA can be reversed by the glutamatergic antagonist, γ-D-glutamylglycine, injected into the NMC, indicating that PIA activation-induced muscle atonia is mediated through the NMC [10] (Fig. 42.2). Indeed, anatomical study using retrograde transport tracer WGA-HRP combined with glutamate immunohistochemistry showed that glutamatergic neurons of the PIA project to the NMC [6]. Using unit recording combined with antidromic stimulation, Sakai et al. [13]

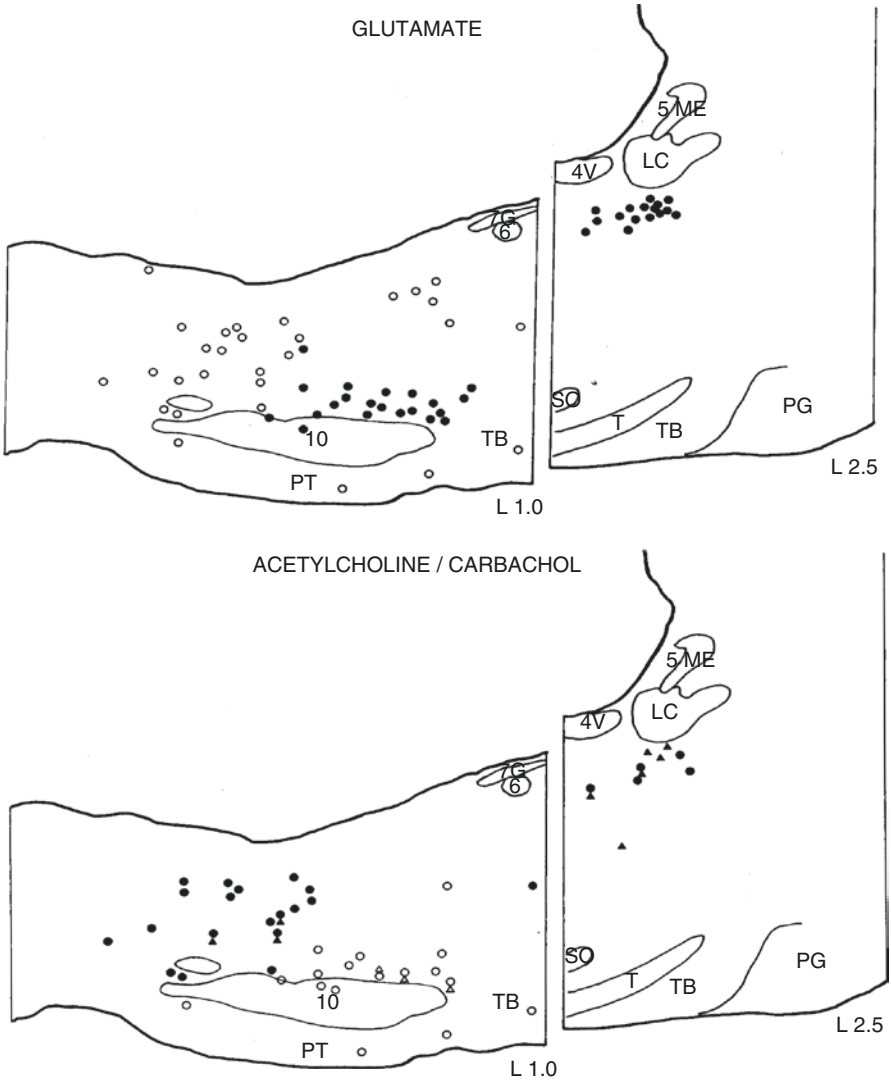

Fig. 42.2 Schematic map of pontomedullary inhibitory areas. Electrical stimulation produced atonia at all the points mapped. The upper and bottom panels represent glutamatergic and cholinergic agonist injection, respectively. Filled symbols (circles and triangles) represent points at which drug injections decreased muscle tone. Open circles represent points at which drug injections increased or produced no change in muscle tone. *4V* fourth ventricle, *5ME* mesencephalic trigeminal tract, *6* abducens nucleus, *7G* genu of the facial nerve, *PG* pontine gray, *PT* pyramidal tract, *SO* superior olivary nucleus, *T* nucleus of the trapezoid body, *TB* trapezoid body (*From Lai and Siegel, J Neurosci 8: 4790–4796, 1988*)

demonstrated that REM-on cells of the pons activate neuronal activity of the NMC during REM sleep. Furthermore, NMC lesions result in REM sleep without atonia [14]. Inactivation of the PIA fails to reduce the inhibitory effect of the NMC stimulation on motor activity [4, 15], indicating that activation of NMC alone is capable of suppressing muscle tone.

The major facilitatory systems in the caudal brainstem projecting to the motor nuclei consist of the lateral portion of the medulla [4], medullary raphe nuclei [16], and noradrenergic locus coeruleus [17]. Inactivation of the facilitatory system may thus suppress muscle tone, as it is seen during cataplectic attacks [18]. However, activation of the inhibitory system or inactivation of the facilitatory system alone may not be sufficient to generate and maintain global muscle atonia during REM sleep. Using the decerebrate preparation and dialysate collection and HPLC analysis, electrical or chemical stimulation was applied in the PIA or NMC; while extracellular fluid was collected from the spinal ventral horn and hypoglossal nucleus by microdialysis, Lai et al. [19, 20] and Kodama et al. [21] demonstrated that an increase in inhibitory neurotransmitters, GABA and glycine, and a decrease in excitatory neurotransmitters, norepinephrine and serotonin, are found in the spinal ventral horn and hypoglossal nucleus.

These results clearly indicated that a combination of activation of the inhibitory system and inactivation of the facilitatory system is required in initiating and maintaining global muscle atonia in REM sleep (Fig. 42.1). The source of GABA and glycine may be the NMC. It has been shown that GABAergic and glycinergic neurons of the NMC project to the spinal cord [22]. The decrease in norepinephrine release in the spinal ventral horn and hypoglassal nucleus may result from the cessation of neuronal firing in the locus coeruleus. Activation of the PIA or NMC has been shown to inhibit neuronal activity of the locus coeruleus [23], which projects to the spinal cord [17]. The decrease in serotonin release during PIA or NMC stimulation may result from activation of the NMC GABAergic neuronal activity, which in turn inhibits the firing of raphe serotonergic spinal projecting neurons [16].

42.3 Brainstem Regions Involved in RBD Generation

While evidence strongly supports the idea that the integrity of the PIA-NMC-spinal ventral horn pathway is required for generating muscle tone suppression during REM sleep, the symptoms of the animals with lesions in this pathway do not fully mimic the symptoms of human RBD. First, idiopathic RBD patients have no change or sometimes longer total time in REM sleep [2], whereas PIA- or NMC-lesioned animals often show massive reduction in REM sleep and/or in the duration of REM sleep episodes [24, 25]. Second, the abnormal motor symptoms in PIA- or NMC-lesioned animals seemed to be limited to REM sleep episodes, while phasic motor activities in NREM sleep, such as periodic limb movements (PLMs) or increased phasic twitches, are prevalent in RBD patients [26]. Thus, an animal model of RBD that expresses all the characteristics of RBD in humans is critically important for understanding the mechanisms underlying all of the manifestations of RBD.

42.3.1 The Caudal Ventral Mesopontine Junction

Based on our study of decerebrate animals, we have speculated that the ventral mesopontine junction (VMPJ) may be involved in the generation of RBD. The VMPJ includes the caudal portion of the dopaminergic retrorubral nucleus,

substantia nigra, and ventral tegmental area (VTA), as well as the ventral paralemniscal tegmental field of the pons. Electrical stimulation of the caudal part of the VMPJ (C-VMPJ) including the ventral paralemniscal tegmental field of the pons and caudal retrorubral nucleus of the midbrain not only suppresses muscle tone during stimulation but also elicits stepping-like activity during interstimulations [5]. Neurotoxic or mechanical lesions of the C-VMPJ generate rhythmic motor activity in the decerebrate animal [27]. Motor hyperactivity induced by lesions of the C-VMPJ can be blocked by APV, a NMDA antagonist, injected into the NMC [28] indicating dysfunction of the C-VMPJ may result in hyperactivity of the NMDA receptors in the NMC, which in turn elicit phasic motor activity. This observation led to the hypothesis that the C-VMPJ plays an important role in the modulation of tonic and phasic motor activity during sleep.

We tested our hypothesis by performing neurotoxic lesions in otherwise intact cats. A small volume (0.5 μL) of high concentration (0.5 M) of NMDA was injected into the C-VMPJ (Fig. 42.3). Sleep and motor activity recordings were performed before and after C-VMPJ lesions. Motor activities including reflex activities, blinking, and walking, as well as behaviors including eating and drinking in wakefulness, appeared normal in the cats after C-VMPJ lesions. However, motor hyperactivities in both NREM and REM sleep were observed after C-VMPJ lesions. Though basal muscle tone remained low, an increase in phasic twitches in the leg, either

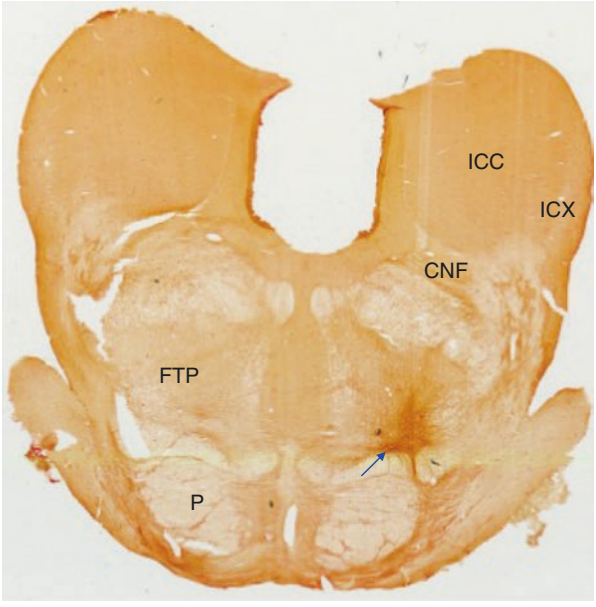

Fig. 42.3 Photomicrograph showing the lesion area (blue arrow) in a cat. Lesions of the ventral paralemniscal tegmental field produce an increase in phasic motor activity in both NREM and REM sleep, REM sleep without atonia, and RBD-like activity. *CNF* cuneiform nucleus, *FTP* paralemniscal tegmental field, *ICC* central nucleus of the inferior colliculus, *ICX* external cortex of the inferior colliculus

unilaterally or bilaterally, during NREM sleep has been observed after C-VMPJ lesions. The changes in phasic leg twitches in NREM sleep can be divided into the early (first week after lesion) and late (after the first week of lesion) phases. Leg twitches in the early phase appeared as irregular and nonperiodic; they are called isolated leg movements (ILM). Then, the isolated leg movements in NREM sleep gradually became more regular and periodic during the late phase of the lesion. Thus, the number of ILM gradually decreased in the late phase after lesion. In contrast, PLMs gradually increased, reached the plateau level at 30 days after lesion, and continued throughout the entire 4-month period of recording.

During REM sleep in these cats, muscle activity appeared as a mixture of intermittent atonia and high muscle tone. PLMs in REM sleep, which are never seen in the normal animals, have also been seen in C-VMPJ-lesioned animals. Simple motor activity or more complex behaviors, such as jerking, kicking and extending of the leg, raising and moving of the head, and lifting of the body, were observed in REM sleep. This abnormal REM sleep behavior, which resembled RBD seen in humans, lasted for 20–62 seconds in each episode. Furthermore, the total time in both NREM and REM sleep was not changed in C-VMPJ-lesioned animals [29]. Taken together, the C-VMPJ-lesioned animals express an unaltered total time in NREM and REM sleep, an increase in PLMs or isolated leg movements in NREM sleep, a mixture of atonia and muscle tone in REM sleep, PLMs in REM sleep, and behavior expressions in REM sleep resembling symptoms in RBD patients.

Thus, the C-VMPJ may play an important role in the neuropathology in RBD. Indeed, abnormality of the ventral pons, but not the dorsolateral pons, has been reported in idiopathic RBD patients [26, 30] (Chap. 9 discusses lesional RBD). Severe neural degeneration in the ventral pons is also reported in olivopontocerebellar atrophy patients, who also develop RBD [31].

42.3.2 The Ventral External Cortex of the Inferior Colliculus (VICX)

The VICX receives inputs not only from acoustic structures such as the superior olivary complex, nuclei of the lateral lemniscus, cochlear nucleus and auditory cortex but also from motor regulating structures including globus pallidus and substantia nigra pars lateralis (SNL) [32]. Neurons from the VICX project to the extrapyramidal system that includes the superior colliculus, pontine nucleus, posterior thalamus, cerebellum, and SNL [33]. Animal studies show that neuronal activity of the C-VMPJ and VICX [34] correlates with vocalization. Electrical stimulations in the VICX increase muscle tone [35]. Both vocalizations and increased muscle tone are seen during dream-enacting motor behavior in REM sleep in RBD patients. Since an extensive reciprocal innervation between C-VMPJ and the VICX, as well as an abnormal auditory brainstem response wave V, which recorded in the inferior colliculus area, have been reported in RBD patients (see citations in [36]), we therefore tested whether the VICX also participates in the generation of RBD. Baclofen, a $GABA_B$ receptor agonist, when microinfused into the VICX, elicits a significant

increase in REM sleep and motor activity in both NREM and REM sleep. PLMs are significantly increased in NREM sleep. REM sleep atonia is intermingled with high muscle tone. RBD-like activities, such as movements of head, leg, and tail and body jerks, are observed in REM sleep during baclofen infusion and 2 hours post-infusion. Low doses of baclofen infused into the VICX have no effect on sleep-wake pattern and motor activity in sleep. In contrast, high-dose saclofen, a $GABA_B$ receptor antagonist, suppresses PLMs in NREM sleep when microinfused into the VICX [36]. The baclofen-VICX-generated RBD-like activity in the rat may be mediated through the anatomical connection to the C-VMPJ.

42.3.3 Sublaterodorsal Tegmental Nucleus of the Rat and Peri-locus Coeruleus α of the Cat

In addition to the rostral ventral pons and caudal ventral midbrain (the caudal VMPJ) in the generation of RBD, the dorsal lateral pons may also participate in the generation of motor hyperactivity in REM sleep. The nucleus in the dorsal lateral pons has been named sublaterodorsal tegmental nucleus (SLD) in the rodent or peri-locus coeruleus α (peri-LCα) in the cat and human. Neurons in the peri-LCα/SLD have been well documented to be involved in REM sleep control. Sakai et al. [13] demonstrated that peri-LCα REM-on neurons, whose activity specifically increased in REM sleep, project to the rostroventral medulla of the NMC, which in turn projects to the spinal cord. The REM-on cells of the peri-LCα/SLD are glutamatergic [37]. Activation of the peri-LCα/SLD by cholinergic or glutamatergic agonists elicited muscle atonia in the decerebrate cat [8, 9]. In contrast, inactivation of the peri-LCα/SLD produced motor hyperactivity in REM sleep in the chronic animals. Adeno-associated viral vectors carrying hairpin (sh)RNAs against *Slc17a6* mRNA (AAV-shvGluT2), a RNA inhibitor targeting vesicular glutamate transporter 2 (vGluT2), injected into the SLD causes REM sleep without atonia, as well as increased phasic motor activities in REM sleep [37].

These motor-behavioral abnormalities in REM sleep seen in the rat with inactivated SLD glutamatergic neurons resemble those found in RBD patients. However, a significant decrease in REM sleep, which is never seen in RBD patients, was observed in the rat after AAV-shvGluT2 injected to the SLD [37]. Furthermore, phasic motor activity in NREM sleep was not reported in the SLD AAV-shvGluT2-injected rat. Thus, disturbance or destruction of SLD glutamatergic neurons may only play a role in the generation of abnormal motor events in REM sleep but not the other components of RBD seen in human patients.

42.4 Hypothetical Link Between Parkinsonism and RBD

It has been shown that idiopathic RBD is a risk factor for developing α-synuclein-related neurodegenerative diseases, such as Parkinson's disease, multiple system atrophy, and Lewy body dementia. Clinical evidence shows that RBD is diagnosed

in 90% multiple system atrophy patients [38] and 50% Parkinson's disease patients [39]. Indeed, patients may be diagnosed simultaneously with Parkinsonian disorders and RBD or diagnosed with RBD before developing Parkinsonian disorders or vice versa [38, 40]. Physiological studies show a prolonged latency of auditory-evoked potential brainstem wave V recorded in RBD, Parkinson's disease [41], and multiple system atrophy [42] patients. Auditory brainstem response waves I–IV interpeak latencies are also significantly prolonged in Parkinson's disease patients [41]. Loss of the dopaminergic neurons in the substantia nigra and noradrenergic neurons in the locus coeruleus has been observed in both Parkinsonism and RBD patients [40]. Transcranial brain sonography assesses that substantia nigra hyperechogenicity exists in both Parkinsonism and RBD patients [43]. Reduced dopamine transporter in the striatum has been also detected in Parkinsonism and RBD patients [44]. However, the reasons for these overlapping symptoms and disease progression have not been explained anatomically.

Alpha-synuclein, a presynaptic protein, is the major component of neuronal Lewy bodies and Lewy neurites. Physiologically, α-synuclein may play an important role in the maintenance and stabilization of fully mature synapses [45]. Pathological changes of α-synuclein result in the loss of its ability to bind to the synaptic vesicle. Abnormal aggregation of α-synuclein forms Lewy bodies and Lewy neurites and leads to synaptic dysfunction and neuron death [46]. Recent studies demonstrate that aggregated α-synuclein can be transmitted from neuron to neuron via anatomical connection [47, 48]. Synthetic α-synuclein preformed fibrils, which act as the seed and cause the aggregation and fibrillization of soluble endogenous α-synuclein, injected into the striatum. Luk et al. [47] report that Lewy bodies and Lewy neurites time and neural connectivity dependently spread from the striatum to the cortex, the thalamus, and the substantia nigra. A caudo-rostral spreading of aggregated α-synuclein has also been reported. With recombinant adeno-associated virus carrying human α-synuclein injected into the vagus nerve, Ulusoy et al. [48] demonstrates that Lewy bodies and Lewy neurites are synaptically transmitted sequentially from the vagus nerve to the vagus motor nucleus of the medulla, the dorsal and ventral nuclei of the lateral lemniscus, the rostral ventral paralemniscal tegmental field of the pons, substantia nigra of the midbrain, and histaminergic system of the diencephalon.

The neural network of Lewy body and Lewy neurite transmission is consistent with clinical findings showing abnormal substantia nigra and structures involved in vocalization and auditory responses, in the nuclei of lateral lemniscus and inferior colliculus. This pathway is also consistent with our animal studies showing RBD is induced by lesions of the C-VMPJ (the rostral ventral paralemniscal tegmental field, Figs. 42.3 and 42.4) in the cat and by VICX-baclofen infusion in the rat (Fig. 42.4). Thus, the C-VMPJ and VICX may play a critical role not only in the generation of RBD but also in the development of Parkinsonism (Fig. 42.4). The upstream connections from the brainstem to the forebrain may originate in the VICX. Anatomical studies show reciprocal innervation between VICX and substantia nigra [33], which in turn reciprocally connect to the striatum. The C-VMPJ may participate in the downstream connection. Reciprocal innervation between the C-VMPJ and NMC,

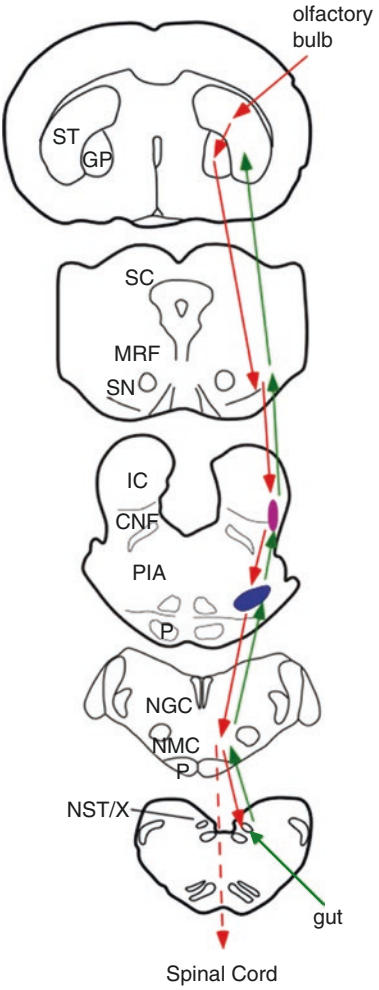

Fig. 42.4 Hypothetical link between Parkinsonism and RBD. Toxic substances ingested into the gut may cause the degeneration of sensory fibers which project to the nucleus of the solitary tract and to the vagus motor nucleus. Similarly, the toxic substances may, via respiration, enter into the olfactory system. Lewy bodies and Lewy neurites formed in the nucleus solitary tract/vagus motor nucleus and olfactory bulb sequentially propagate from neuron to neuron. Depending on the neural structures affected by Lewy bodies and Lewy neurites, patients may develop RBD and then Parkinsonism or vice versa. See the text for the details. The pink and blue areas represent the ventral external cortex of the inferior collicus and the caudal ventral mesopontine junction area, respectively. *GP* globus pallidus, *IC* inferior colliculus, *MRF* mesencephalic reticular formation, *NST/X* nucleus solitary tract/vagus motor, *SC* superior colliculus, *SN* substantia nigra, *ST* striatum

the NMC and the nucleus of the solitary tract, as well as the C-VMPJ and the nucleus of the solitary tract has also been reported [49, 50].

We hypothesize that neuronal degeneration can be initiated in either part of the central nervous system and progressively extend to the caudal or rostral part of the brain. Patients may be diagnosed with RBD first and then developed Parkinsonism when neurodegeneration begins in the C-VMPJ. Lewy bodies and Lewy neurites in the C-VMPJ are then propagated rostrally to the VICX, substantia nigra, and striatum. Alternatively, Lewy bodies and Lewy neurites may caudo-rostrally and rostro-caudally serve as a conduit from the vagus motor nucleus and the olfactory bulb. Thus, Parkinsonism and RBD may be diagnosed simultaneously. In contrast, when patients were diagnosed with Parkinson's disease first and then develop RBD, it may be a result of differential timing in the progression of Lewy body and Lewy

neurite transmission from the rostral to the caudal brain and from the caudal to the rostral brain, with the prorogation rate from the olfactory bulb to the substantia nigra being higher than from the vagus motor nucleus to the C-VMPJ.

Conclusions

Muscle atonia in REM sleep results from the activation of the medial pontomedullary reticular formation, which in turn activates the NMC GABAergic and glycinergic neurons and inhibits medullary raphe serotonergic and pontine locus coeruleus noradrenergic neuronal activity. The neurodegeneration of the medial pontomedullary reticular formation causes solely REM sleep without atonia and abnormal motor activity in REM sleep. In contrast, the rostral part of the brainstem is not only involved in the modulation of tonic muscle activity in REM sleep via the connection of PIA-NMC pathway, but also in the inhibition of phasic motor activity in NREM and REM sleep. Dysfunction of the rostral brainstem, the C-VMPJ and VICX, elicits RBD. Anatomical connections innervating the C-VMPJ and VICX may play an important role in the development of Parkinsonism in idiopathic RBD patients and vise versa.

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REM Sleep Behavior Disorder: The Link Between Synucleinopathies and REM Sleep Circuits

43

Dillon McKenna and John Peever

43.1 Introduction

REM sleep behavior disorder (RBD) is a neurological condition that afflicts more than 1% of the general population and is primarily diagnosed in men over the age of 60 [1–3]. Symptoms of RBD include a loss of skeletal muscle paralysis (atonia) during REM sleep coupled with outbursts of motor behaviors [4–7]. RBD-related movements can vary from excessive muscle twitching and limb jerking to intricate behaviors related to reported dream content [8]. These "dream-enacting" behaviors consist of talking and culture-specific gesturing and frequently include punching and kicking [8, 9]. While these behaviors pose a risk of injury to the patient and/or their bed partner, these motor symptoms can usually be successfully suppressed with melatonin and/or clonazepam [6]. However, RBD is still a major health concern because the vast majority (>80%) of RBD patients are eventually diagnosed with some form of synucleinopathy, such as idiopathic Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy [4, 10, 11].

Waking motor dysfunction associated with synucleinopathies primarily arises with degeneration of the midbrain substantia nigra (a major source of dopamine for the brain), while degeneration of the neocortex is associated with cognitive impairment and dementia [12]. Synucleinopathic brains show neurodegeneration in the presence of prominent and dense intracellular protein inclusions called Lewy bodies, which are linked to alpha-synuclein (αSyn), which is a major component in Lewy bodies [14], highlighting the important role that αSyn likely plays in these neurodegenerative diseases.

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While RBD can emerge with recognized causes, including brainstem injury, alcohol withdrawal, antidepressant usage, narcolepsy, or RBD occurring concurrently with neurodegenerative disease, many cases emerge with no identified origin, and this "idiopathic" RBD is one of the best known predictors of synucleinopathies [15]. The high frequency with which synucleinopathy diagnosis follows idiopathic RBD symptoms suggests that RBD itself results from synucleinopathies [4, 6, 15–17]. Additionally, the motor symptoms of RBD increase in severity over time [18], and RBD patients show slowing of cortical activity, an early marker for cognitive impairment [19], which further suggests RBD could be an early and progressive component of neurodegenerative disease. This progression is in-line with the staging of Parkinson's disease pathology, with degeneration seen early in the caudal brainstem before advancing rostrally alongside emerging Parkinsonian symptoms [12, 20]. Indeed, the location of the neural networks responsible for suppressing muscle activity during REM sleep is located within the brainstem, specifically in regions that show pathological αSyn deposits and cell loss in the brains of patients with synucleinopathies [12, 20].

This chapter explores the hypothesis that RBD symptoms are caused by synucleinopathic degeneration of the brainstem regions controlling muscle activity during healthy REM sleep. Here, we will discuss (1) the brainstem mechanisms that control healthy REM sleep atonia, (2) the animal models used to study REM sleep circuit function and RBD mechanisms, (3) the changes in the structure and function of brainstem regions in RBD patients, and (4) new insights into the mechanisms of synucleinopathies and their potential link to RBD development. Understanding the pathogenesis of RBD could lead to understanding the progression of synucleinopathic neurodegenerative diseases and in turn lead to neuroprotective strategies for slowing or halting disease progression.

43.2 The Brainstem Circuits that Control Muscle Atonia During REM Sleep

In order to understand the mechanisms underpinning the excessive muscle activity in RBD, it is necessary to first understand how REM sleep atonia is normally generated during healthy sleep. In this section, we outline the core circuitry responsible for generating REM sleep atonia.

During normal REM sleep, skeletal muscle activity (with the exception of respiratory, inner ear, and extrinsic eye muscles) is actively inhibited, thus forcing skeletal muscles into a state of motor paralysis [21–23]. During REM sleep paralysis, the somatic motoneurons that innervate skeletal muscles are strongly inhibited by hyperpolarizing signals [24, 25]. Motoneuron hyperpolarization results from a combination of inhibitory neurotransmitters, namely, gamma-aminobutyric acid (GABA) and glycine. Simultaneous blockade of both GABA and glycine receptors on motoneurons prevents muscle paralysis during REM sleep [22, 23].

The source of GABA and glycine signals onto motoneurons during REM sleep originates from inhibitory neurons within the ventromedial medulla (VMM) as well as from interneurons within the spinal cord [22, 26–31]. Neurons within the VMM have been shown to project to motoneurons [32], and they are most active during

REM sleep as evidenced by cellular recordings and by expression of c-Fos (an immunohistological index of neuronal activity) [33, 34]. Stimulation of the VMM region not only causes the release of both GABA and glycine onto motoneurons, but it also causes the inhibition of muscle activity in waking animals [27, 35]. In addition to the VMM, genetic silencing of GABA and glycine signaling from spinal interneurons result in heightened motor activity during REM sleep, indicating that REM sleep paralysis is caused by both spinal interneurons and those in the VMM [36].

Inhibitory neurons within the VMM and spinal cord are activated during REM sleep by a "master switch" that generates both REM sleep and REM sleep atonia. The REM sleep "master switch" is located in the dorsal pons and in an area known as the subcoeruleus (SubC), also called the sublaterodorsal tegmental nucleus (SLD). Different populations of cells in the SubC region are responsible for generating both REM sleep itself and muscle atonia during REM sleep because lesions of the SubC alter the amount of REM sleep and also cause a loss of REM sleep atonia [22, 37, 38].

The SubC region contains multiple types of neurons that release either GABA, glutamate, or acetylcholine. However, multiple studies using c-Fos expression, unit recordings, and calcium imaging show that glutamatergic neurons within the SubC are most active during REM sleep [37–41], suggesting that these particular neurons generate REM sleep. In addition, glutamatergic neurons in the SubC project to both the VMM and spinal interneurons, suggesting they are also involved in generating REM sleep paralysis [31, 36–38].

While more rostral brain areas have also been implicated in modulating REM sleep [42–46], the circuit outlined above appears to form the "core" circuit responsible for generating REM sleep paralysis because when lesioned it results in the primary motor symptoms observed in human RBD patients. Therefore, recent basic science data indicate that glutamatergic SubC neurons are active during REM sleep and by virtue of their excitatory projections to the GABA/glycine neurons in the VMM and spinal interneurons cause inhibition of motoneurons and hence skeletal muscle inactivity during REM sleep (Fig. 43.1).

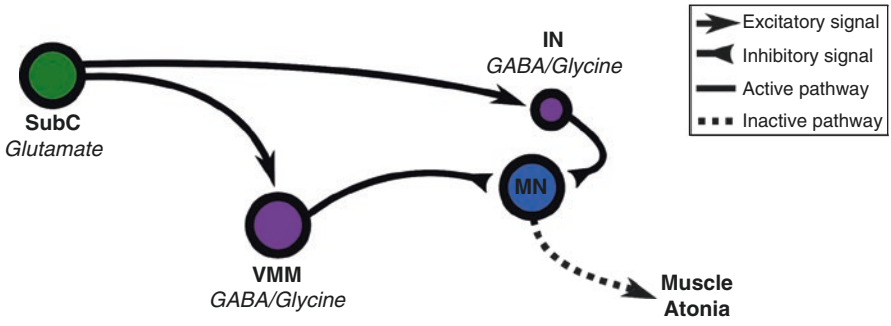

Fig. 43.1 Hypothesized brainstem circuit controlling normal REM sleep atonia. The pontine subcoeruleus (SubC) and ventromedial medulla (VMM) make up the "core" of the circuit that suppresses muscle activity during REM sleep. During REM sleep, glutamatergic SubC neurons are active and project excitatory signals to gamma-aminobutyric acid (GABA) and glycine neurons in the VMM and spinal interneurons (IN). These regions then project inhibitory, hyperpolarizing signals to somatic motor neurons (MN), silencing their activity and paralyzing the muscles they innervate

43.3 Modeling RBD in Animals

Animal models have been integral for understanding how normal REM sleep atonia is generated and for understanding the pathophysiology of RBD. Manipulation of specific brain nuclei across several species has allowed basic science researchers to elucidate the circuitry controlling REM sleep atonia and has helped generate the hypothesis that damage to a restricted region—i.e., the SubC—contributes to generating the motor behaviors associated with RBD.

Prior to RBD being identified in humans, an RBD-like loss of muscle atonia accompanied by dreamlike-enacting behaviors ("oneirism") was observed in cats following lesions to the dorsal pontine tegmentum that encompasses the SubC [47]. Lesions of the SubC resulted in motor behaviors during REM sleep that included simple limb jerks or complex movements such as walking, leaping, or "hunting" [28, 29, 47]. These experiments helped identify the region of the brainstem containing the SubC as necessary for suppressing muscle activity during REM sleep, an idea supported by similar findings in rodents [31, 48, 49]. As previously observed in cats, both rats and mice with cell-body specific lesions of the SubC displayed loss of REM sleep atonia along with the emergence of complex movements such as chewing and walking during REM sleep [31, 48, 49]. Taken together, the results of these experiments helped show that damage to the SubC region could result in loss of REM sleep paralysis and produce complex movements without the need for dysfunction at the level of the cortex, supporting the hypothesis that damage at the level of the brainstem could be the root cause of RBD.

Recent technical advances in neuroscience are now affording biologists the ability to genetically target and modulate the activity of specific cell types, and this has led to the demonstration that glutamatergic cells in the SubC are imperative for suppressing muscle activity in REM sleep. When SubC glutamatergic neurons were genetically silenced during REM sleep, mice showed heightened muscle twitches and loss of paralysis with overt movement behavior [36]. Furthermore, genetically targeted expression of light-sensitive ion channels, which allows the temporally controlled manipulation of SubC glutamatergic neuron activity, has shown that inhibition during REM sleep prevents muscle atonia, whereas increased glutamatergic cell activity strengthens atonia [50]. Together, these experiments in animal models show that glutamatergic SubC neurons are needed for suppressing muscle activity during normal REM sleep and demonstrate the likelihood that degeneration of this region, and specifically of glutamatergic cells, could underlie the motor symptoms of RBD.

Cells in the VMM are located caudally to the SubC, and they have been shown to play a role in generating RBD behaviors in animals. Lesions encompassing the VMM in both cats and rats induced excessive limb jerking and complex movements in REM sleep [28, 30]. However, selective silencing of GABA and glycine transmission from the VMM in mice prevented muscle paralysis without causing complex movements [50, 51]. Therefore, these experiments further support the idea that degeneration of the core REM sleep atonia circuit may underlie the heightened muscle activity seen in RBD. However, the lack of overt movement after blocking

inhibitory signals from the VMM in mice could indicate that damage at the level of the SubC is more important for eliciting the full range of motor symptoms in RBD.

RBD motor symptoms can also be elicited in mice that have genetically altered GABA and glycine signaling. Mice lacking functional GABA and glycine neurotransmission show complex activities such as grooming and walking during REM sleep, and, as in human RBD patients, these motor symptoms are suppressed by both melatonin and clonazepam [22]. This model could relate to alcohol withdrawal or related cases of acute RBD, as in these circumstances RBD symptoms may arise from substance-related imbalances in neurotransmission, as postsynaptic GABA receptors are downregulated in chronic alcoholism and during alcohol withdrawal [52, 53].

Midbrain circuits have also been implicated in controlling motor activity during REM sleep. Lesions of dopamine cells in the substantia nigra (a midbrain region associated with Parkinson's disease [54]) in marmoset monkeys caused a lack of muscle atonia in REM sleep, but did not impact the phasic muscle twitches during REM sleep nor did they produce the more complex movements associated with RBD [55]. However, lesions of the substantia nigra in rats did not affect muscle activity while in REM sleep [56], suggesting that degeneration of structures rostral to the SubC and VMM circuits are not responsible for REM sleep atonia and are unlikely to be the root cause of RBD. However, because motor behaviors typically worsen over time in RBD [18] and because patients with RBD show degeneration of dopamine cells in the substantia nigra [4, 57], it is possible that loss of midbrain dopamine cells could also contribute to motor dysfunction in RBD.

43.4 The Link Between Brainstem Pathology and RBD

Animal research clearly demonstrates that damage to brainstem structures that generate REM sleep is associated with RBD-like behaviors in cats, rats, and mice. However, examining cases where humans developed RBD secondary to a known medical condition has also helped to illuminate potential mechanisms of RBD. For example, RBD is associated with tumors, strokes, or injury to areas in the pontine tegmentum encompassing the SubC region [10, 58–61]. Chapter 9 comprehensively addresses this topic. Therefore, both basic science research and clinical case reports indicate that the dorsal pons, and most notably the SubC region, are necessary for motor inactivity during REM sleep and that injury to this region is sufficient for causing loss of motor atonia in RBD.

Imaging studies have also been instrumental in shedding light on brain abnormalities in RBD patients (Chap. 30 extensively covers brain imaging in RBD). For example, imaging of neuromelanin (a pigment found in cells) in RBD patients with and without other known comorbidities showed signs of depigmentation in an area of the SubC and that the level of depigmentation is positively correlated with the severity of REM sleep without atonia [62, 63], suggesting that RBD is associated with damage or degeneration of the pontine cells that generate REM sleep atonia. In addition, postmortem examination of brain tissue from RBD patients with Parkinson's disease revealed the presence of Lewy bodies and cell loss in the SubC

and VMM regions, further indicating that degeneration of these REM sleep-controlling areas is associated with RBD [4, 16, 57].

Therefore, cumulative evidence points toward the fact that damage to, or degeneration of, the brainstem circuits that control healthy REM sleep are likely contributors to the motor symptoms of RBD. As well, the signs of αSyn deposition in REM sleep-controlling regions in synucleinopathies [4, 64], along with signs of damage in idiopathic RBD, suggest synuclein-related degeneration of these regions is the root cause of RBD.

43.5 The Link Between Synucleinopathy in the Brainstem and RBD

Long-term monitoring of idiopathic RBD patients has revealed that 80–90% of patients eventually develop some form of synucleinopathy [4, 10, 11]. The fact that RBD is such a strong predictor of synucleinopathies, combined with postmortem evidence showing cell loss and aggregated αSyn in the brainstem areas that generate REM atonia regions, has led to the hypothesis that idiopathic RBD is itself a disorder that results from the same mechanisms that underlie synucleinopathies [4, 6, 15–17].

While evidence from both animal and human data has shown that damage to the brainstem underlies the symptoms of RBD, there is currently no definitive evidence showing that synucleinopathic degeneration of these circuits underlies idiopathic RBD. However, there is new evidence concerning the mechanisms of how synucleinopathies cause neurodegeneration and how such mechanisms could contribute to RBD pathogenesis.

αSyn is an endogenous protein located within healthy brain cells. While the major function of αSyn is undefined, it is clear that it is located within synaptic terminals of mature neurons [65, 66] and that suppression of αSyn expression reduces the supply of synaptic vesicles [66], suggesting αSyn may play a role in transmitter release. Healthy αSyn contains several α-helices at the N-terminus [67], which is altered in Parkinson's disease-related mutations to form β-sheets that are highly susceptible to aggregation [13, 68]. Also, mutated αSyn tends to build-up within cells because the pathway involved with the normal clearance of αSyn is less effective in its mutant form [69]. In addition to mutations, the overexpression of unmutated αSyn is also associated with aggregation and cell loss. Gene duplications and triplications have been linked to heritable Parkinson's disease, with triplication connected to earlier disease onset [70, 71].

The role that αSyn aggregates play in neurodegeneration is unknown; however, αSyn and cellular oxidative stress have been linked to degeneration. In vitro, neurons that overexpress αSyn have mitochondrial dysfunction, with enlarged mitochondria and increased levels of free radicals, which are signs of oxidative stress [72]. Also, mice with the αSyn gene eradicated are resistant to 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) induced neurodegeneration, a model of Parkinson's disease that causes oxidative stress through mitochondrial dysfunction

that induces cell death [72]. Therefore, while it appears to serve an endogenous function in the brain, αSyn can also be toxic, especially in misfolded and aggregated forms. How this process of misfolding and degeneration develops in the brain is unclear; however, recent research has demonstrated how this pathogenic protein may spread throughout the brain in a cell-to-cell manner.

Multiple lines of evidence point toward misfolded αSyn as the root cause of degeneration that results in the spread and progression of degeneration through the brain in synucleinopathies. Postmortem analysis of patients diagnosed with Parkinson's disease, along with non-symptomatic controls, revealed a progression of αSyn pathology in the brain [12, 20]. In fact, a number of non-symptomatic brains displayed early signs of αSyn plaque formation and cell loss in the caudal brainstem, specifically the medullary dorsal motor nuclei of the glossopharyngeal and vagus nerves [12]. In patients with more advanced Parkinson's disease, this pathology seemed to have progressed rostrally, also affecting medullary and pontine regions that include the SubC and VMM [12, 20, 64]. Patients with more severe waking movement impairments had Lewy bodies and abundant degeneration of midbrain substantia nigra dopaminergic neurons, while patients with cognitive impairment or dementia also displayed degeneration of the neocortex [12]. This led to the proposed staging of Parkinson's disease, and the idea that pathology related to αSyn could progress in a cell-to-cell fashion, with the brainstem areas containing the REM sleep atonia circuitry facing degeneration early in disease development [12, 20] (Fig. 43.2).

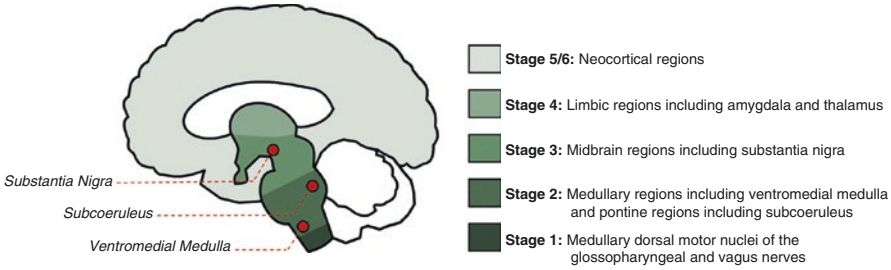

Fig. 43.2 Apparent progression of αSyn pathology in Parkinson's disease. (*Left*) sagittal view of the human brain, with color corresponding to (*right*) stage of disease pathology. Following postmortem analysis of patients diagnosed with Parkinson's disease (PD) or non-symptomatic controls, Braak et al. observed that a number of non-symptomatic brains displayed signs of αSyn plaque formation and cell loss in the medullary dorsal motor nuclei of the glossopharyngeal and vagus nerves (stage 1). In patients with more widespread pathology, the presence of Lewy bodies seemed to have progressed forward in the brain, also affecting the more rostral ventromedial medulla (VMM) and pontine regions that included the subcoeruleus (SubC) (stage 2). Patients with waking movement impairments classically associated with PD had Lewy bodies and abundant degeneration of midbrain substantia nigra (SN) dopaminergic neurons (stage 3), while patients with cognitive impairment or dementia also displayed degeneration and aggregates in the neocortex (stage 5/6). This progression of symptoms and pathology lines up with the progression of RBD to PD diagnosis, with the REM atonia circuitry affected early in disease development. The location of core REM sleep circuitry (VMM and SubC) along with the location of the SN is highlighted

The proposed ability of toxic αSyn to propagate through connected regions has been supported by investigation of Parkinson's disease patients who received grafts of embryonic fetal tissue. In an attempt to restore dopamine transmission, these patients received grafts from embryonic mesencephalic neurons into their substantia nigra [73]. Remarkably, upon postmortem examination, the previously healthy grafted tissue showed signs of aggregated αSyn pathology that increased with time, demonstrating the possibility that misfolded αSyn could spread into previously healthy tissue [74] and supporting the theory that synucleinopathies progress by a cell-to-cell mechanism.

This proposed cell-to-cell transmission of misfolded αSyn was first demonstrated experimentally by Luk et al. using a single injection of misfolded αSyn aggregated fibrils into the brains of mice [75]. Following injection of preformed alpha-synuclein fibrils, they observed what appeared to be an infectious spread of αSyn misfolding, recruiting endogenous αSyn to misfold and aggregate, resulting in cell loss in dopaminergic regions and motor symptoms resembling Parkinson's disease [75]. These findings were supported by later experiments by Recasens and colleagues using extracts of Lewy bodies from human Parkinsonian brains [76]. When injected into the brains of both mice and macaque monkeys, it was found that the human αSyn entered into host cells and caused a progressive loss of dopaminergic neurons [76].

The demonstration that misfolded αSyn moves in a cell-to-cell fashion is potentially important for understanding the development of idiopathic RBD. Along with data showing the apparent caudal to rostral progression of Parkinsonian pathology, these findings suggest early misfolded αSyn could first invade and degenerate the brainstem circuits that trigger REM sleep atonia and then spread to the rostral brain regions that are classically associated with synucleinopathies and their clinical expression [4, 6, 15–17].

However, very recent experimental data now suggest that αSyn-mediated dysfunction of the circuits that generate REM sleep atonia could underlie RBD. McKenna and Peever used a recombinant adeno-associated virus to drive expression of human αSyn in the SubC region of healthy mice. They not only found evidence for aggregation of αSyn within SubC cells 8 weeks after inoculation but that mice also began to display heightened motor activity selectively during REM sleep. They found no evidence for altered motor behaviors during either non-REM sleep or during wakefulness, suggesting that SubC dysfunction leads to RBD-like behaviors. In addition, they found evidence for cortical EEG slowing that is reminiscent of that observed in human RBD patients [19]. Detailed histological analysis revealed the presence of phosphorylated αSyn within SubC cells, which is a sign of the aggregated form of αSyn that is classically associated with Lewy bodies and neuronal toxicity [77].

Together, these findings suggest that pathological αSyn accumulation within the core REM sleep circuits can produce some of the classic features of human RBD. However, what remains to be determined is whether pathogenic αSyn will spread rostrally and invade the dopamine circuits that underlie Parkinson's disease. Additionally, the question of why REM sleep-generating cells are initially targeted and vulnerable to synucleinopathic degeneration remains to be determined. This is an important question for understanding the pathogenesis of RBD, because halting the initial invasion of REM sleep-generating cells could ultimately prevent the cell-to-cell transmission of misfolded αSyn and thus prevent the progression of further neurodegeneration that leads to Parkinson's disease and other synucleinopathies.

Conclusions

Here, we outlined the connection between RBD, the circuits that function to trigger muscle atonia during REM sleep, and how synucleinopathic degeneration of these circuits could lead to RBD. RBD results from excessive motor activity during REM sleep. The most parsimonious explanation for this motor symptom is that the circuits that produce REM sleep atonia are dysfunctional because they have degenerated or have been damaged. The link between brainstem degeneration and RBD stems from the observation that >80% of idiopathic RBD patients eventually develop some form of synucleinopathy, which themselves reflect degeneration in the brainstem. Animal models have shown that lesions of the REM sleep circuitry produce RBD-like behaviors, and postmortem evidence indicates that Lewy pathology is present in homologous brain regions in RBD patients. Recent evidence shows that pathological αSyn triggers Lewy pathology by spreading throughout the brain in a cell-to-cell fashion. It is therefore likely that RBD arises from the same pathogenic mechanisms that underlie synucleinopathies, with disease processes beginning in the brainstem, where REM sleep atonia is controlled, before progressing rostrally to the structures whose degeneration results in the classic motor and cognitive symptoms associated with synucleinopathies (Fig. 43.2).

We propose that the majority of cases of RBD are caused by the same disease processes that underlie synucleinopathies and that RBD is not a separate clinical entity from these disorders, rather it is one of the earliest detectable symptoms of them. In support of this proposal are two reports of Lewy body disease detected at autopsy in patients with idiopathic RBD followed longitudinally until the time of death from pneumonia [57, 78]. An 84-year-old Japanese man with a 20-year history of idiopathic RBD, PSG-confirmed, who responded to clonazepam therapy. Parkinsonism and cognitive deficits were never detected. He died of pneumonia at age 86 years. Autopsy findings confirmed severe Lewy body disease with marked loss of brainstem monoaminergic neurons in the LC and SN. A 57-year-old man with a 15-year history of idiopathic RBD, PSG-confirmed, who responded to clonazepam therapy. He died of pneumonia at the age of 72 years. Histopathology confirmed Lewy body disease, but the SN and LC did not have significant neuronal loss or gliosis, despite the presence of Lewy bodies.

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Part VI

Challenges and Opportunities

Toward Disease Modification Trials in RBD: Challenges and Opportunities

44

Aleksandar Videnovic and Birgit Högl

44.1 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia that evolves into one of the synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA), in over 90% of cases [1, 2]. Despite the development of pharmacological and surgical therapies for these disorders, the goal of slowing the disease progression has not been achieved. While numerous preclinical studies demonstrated neuroprotective effects of various compounds, no clinical trial to date has demonstrated disease-modifying effects for any of synucleinopathies. This is thought to be a result of many factors, including reliance on animal model data that do not capture the true nature of a neurodegenerative process in humans, imperfect trial designs, inadequate patient selection, and unsuitable trial end points [3].

Given the high conversion rates of RBD to a synucleinopathy, the RBD population is positioned to serve as the ideal study population for testing promising agents that may arrest synuclein-specific neurodegenerative process. Recent progress related to the better understanding of the pathophysiology of RBD, its progression into synucleinopathies, and acquired knowledge about markers of synuclein-specific neurodegeneration within the RBD phenotype have built a foundation for the

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development of clinical trials targeting disease modification [4–6]. Further, diagnostic algorithms for RBD are improved, and polysomnography (PSG), if carefully performed from a technical standpoint, provides an accurate and quantitative assessment of the disorder [7]. We are therefore presently at an opportune time to start developing protocols for such clinical trials. The International RBD Study Group (IRBD-SG) has published a consensus statement on devising symptomatic studies in RBD and studies of neuroprotection against Parkinson's disease (PD) and related neurodegeneration in RBD. The consensus was published after the 4th annual IRBD-SG meeting held in Marburg, Germany, in 2011 [8].

Lessons learned from clinical trials centered on disease modification in Parkinson's disease are valuable for the planning of similar trials in the RBD population. A majority of disease-modifying clinical trials in PD utilized clinical end points and/or surrogate markers, which may have impacted results leading to a negative trial [9]. The study designs utilized in these trials also have stymied the chance for capturing disease modification effects [9]. Distinguishing disease-modifying effects from a symptomatic treatment effect of a tested compound has been one of the obstacles in PD trials performed to date. A major challenge when it comes to planning disease-modifying clinical trials in the RBD population is the overall lack of clinical trial experience in the RBD population. Other important considerations for these clinical trials encompass various diagnostic aspects of RBD, approaches needed for effective and robust screening, selection of inclusion and exclusion criteria, as well as primary and secondary end points. In this chapter we outline these pivotal considerations for the planning of a clinical trial that will center on disease modification in RBD.

44.2 Recruitment

Estimated prevalence rates of RBD range 0.5–2% [10–12]. Given this low prevalence of the disorder, meeting the recruitment goals in disease-modifying trials must be carefully planned. This is further challenged by the likely presence of multiple, sometimes simultaneous, clinical trials with the same goal. Moreover, individuals with RBD who have been exposed to an experimental agent with potential disease-modifying properties may not be eligible for participating in another trial for a certain period of time or even indefinitely. International collaborations, such as those spearheaded by the IRBD-SG, will be helpful in overcoming some of the challenges related to recruitment into neuroprotective trials (for a detailed description of the IRBD-SG, please refer to Chap. 3). The recruitment efforts will need to be spread beyond the academic membership of the IRBD-SG and will involve a broad network of neurologists and sleep, movement, and dementia specialists, along with associated relevant patient-centered foundations and advocacy groups. Efforts to increase awareness about RBD will certainly have further positive impact on patients' recruitment into these clinical trials.

44.3 Diagnostic Aspects of RBD and Screening

Effective screening methods with excellent accuracy will be a critical step in disease-modifying trials targeting the RBD population. Currently, loss of muscle atonia during REM sleep documented via overnight PSG on the background of dream enactment is required to establish the diagnosis of RBD. PSG is cumbersome and costly, which limits its use in broad screenings of potential trial participants. Several RBD questionnaires have been developed and validated in the RBD population [13–17]. The enthusiasm for their use is somewhat dampened by their low specificity for RBD and poor performance when applied within the general population. While the diagnostic value of these questionnaires is suboptimal, its utility as a screening tool for RBD is promising and practical (discussed in detail in Chap. 19). Recruitment/screening processes for disease modification trials in RBD will need to be broad and will likely encompass methods such as radio/TV/newspaper advertisements as well as telephone interviews with prospective participants.

44.4 Study Population Selection (Inclusion/Exclusion Criteria)

A selection of appropriate study population is vitally important for any clinical trial. Common failures of PD trials aimed at disease modification have been in part contributed by heterogeneous study populations, which may have diluted effects of investigational agents [3]. The intrinsic heterogeneity of individuals with RBD manifesting as differences in gender, disease duration, and coexistence of additional markers of neurodegeneration has to be embraced when planning a clinical trial centered on disease modification.

Considerations that pertain to the selection criteria for a disease-modifying clinical trial compared to a treatment, symptomatic trial in the RBD population have many similarities but also important differences. This stems from different objectives between these two types of clinical trials in RBD. For example, the severity and frequency of dream enactment and concomitant treatments are very relevant to consider when crafting a protocol for a symptomatic trial [8]. These aspects are much less relevant for a trial that aims to alter progression of neurodegeneration. For the latter trial, it is more important to select individuals, who, besides dream enactment, harbor additional markers of ongoing neurodegeneration, such as constipation, olfactory deficits, and neuropsychiatric symptoms, to name a few. Careful consideration of these aspects will improve the feasibility of a trial by increasing the likelihood of achieving a phenoconversion to a synucleinopathy within the trial duration. An excellent understanding of the nature of these neurodegenerative biomarkers, which is a topic discussed throughout this book, is a prerequisite for the development of a well-designed clinical trial protocol [6].

44.5 Clinical Trial End Points

Proper selection of the primary end points and having appropriate trial design are likely the two most important aspects for clinical trials. The selection of the primary end point for a disease-modifying trial within the RBD population is challenged by possible conversion of RBD into different synucleinopathies with different phenotypes. This has a large impact on the selection of the primary outcome metric. For example, a conversion to PD will be heralded by the presence of motor signs, while the development of DLB will be manifested by emergence of a distinct cognitive profile. These challenges may be avoided by not choosing clinical end points. Instead, a dynamic biomarker that will be sensitive to capture the effects of an investigational agent on the progression of the neurodegeneration may be the ideal end point for disease-modifying trials in RBD. Dopamine transporter (DaT) imaging of nigrostriatal system has been characterized as a sensitive biomarker of neurodegeneration in RBD [18, 19]. It is presently one of the best candidates for a primary end point in disease-modifying trials targeting the RBD population. In addition to good predictive properties for imminent parkinsonism in individuals with RBD that is relevant for a trial duration, DaT scans can also be used in the screening process to assure the selection of study participants with evidence of an abnormal dopaminergic system with likely conversion within the proposed trial duration. Identification of additional biomarkers sensitive to changes within the neurodegeneration cascade is an important future goal. Development of a ligand for in vitro imaging of alpha-synuclein will certainly represent a breakthrough in quantifying disease progression across synucleinopathies. Quantitative assessment of motor performance and sleep metrics, such as REM sleep without atonia, may be considered as surrogate end points as well. Their usefulness in this regard will be improved by ongoing efforts to better understand how these metrics change throughout the evolution of neurodegeneration.

44.6 Clinical Trial Design

The field of RBD has lacked well-designed, large-scale, randomized, blinded clinical trials. A double-blind, randomized, placebo-controlled, parallel-arm clinical trial of nelotanserin is currently ongoing in subjects with DLB or PDD who have RBD. The trial will provide valuable insights relevant to trial planning and execution within the RBD population (NCT02708186; clinicaltrials.gov). Numerous trial designs have been employed in the study of disease modification in PD [20]. Lessons learned from these trials should influence planning for trials in RBD. Study designs employed in PD clinical trials encompass washout design, delayed-start design, futility designs, as well as designs that assess either time to an event or a change in rating scale over time as end points. Each of these designs had advantages but also disadvantages that resulted in difficulties with the interpretation of study findings. Several PD trials employed surrogate imaging markers of the nigrostriatal system, specifically PET imaging as a measure of dopa decarboxylation and SPECT imaging of the dopamine

transporter [21, 22]. While initially promising, use of surrogate markers proved to have its own challenges since the investigational agents themselves interacted with imaging radioligands that affected the interpretation of results from these trials. Novel techniques such as clinical trial simulation and disease modeling have been employed in PD in recent years with goals to reduce errors in trial design to enable investigators in selecting an appropriate clinical trial design [23].

44.7 Clinical Trial Duration

A phenoconversion of RBD to a clinically manifest synucleinopathy may take many years. This has impact on the duration of a clinical trial that aims to examine disease modification. From feasibility perspectives, the duration of disease modification trials should take into consideration many economic and logistical factors and not exceed 5 years. At the same time, the trial duration must be sufficiently long enough to allow the proper ascertainment of expected treatment effect. Available data on phenoconversion rates from several longitudinal cohorts of patients with RBD will guide selection of study participants with projected phenoconversion within a time frame of the trial. Continuing follow-up of these cohorts will continue to refine data that will inform selection of study participants and overall trial designs.

44.8 Stages of Clinical Development

Traditionally, an investigational compound goes through several stages of clinical development that span phase I–III clinical trials before it is approved for therapeutic use. This lengthy and costly process assures proper safety of the tested compound, followed by ultimate efficacy testing in a phase III trial. Considering that RBD represents a continuum of a neurodegenerative process, it is possible that some of the traditional phases of drug development may not be needed, which may shorten a drug development cycle. This scenario is only relevant for drugs already tested/used in synucleinopathies with established safety and pharmacokinetic profiles. Other compounds with unknown adverse event profiles will need to be rigorously studied from a safety standpoint as they will be taken for many years or even decades. Another complexity of a disease modification trial in RBD is its likely international nature. Since such a trial will be run across many countries, a significant amount of work will need to be done in order to meet all the regulatory requirements that each country has.

Conclusions

In summary, we are at an opportune time to initiate planning for disease modification trials for synucleinopathies, and the RBD population is an ideal study population for the testing of promising investigational compounds. While the work done so far on RBD and its progression into clinically manifest synucleinopathies represents an excellent foundation for planning of disease modification trials, much

yet has to be accomplished before such trials commence. Some aspects of further work that has to be done should center on a better understanding of the heterogeneity within the RBD population. To that end, there is a need for stratification within the RBD clinical trial population by using clinical, genetic, and biochemical markers. Progression of neurodegenerative processes in RBD may not be linear, which has significant implications for disease modification approaches. Recently proposed research diagnostic criteria for prodromal PD hold great promise for promoting disease modification therapies. Some concerns exist since detection of individuals with prodromal PD and other synucleinopathies requires resource-limited and specialized procedures, which affects feasibility of these efforts. Further work needs to be done on optimization of end points and clinical trial designs for demonstrating disease modification. We should also embrace rapidly developing mobile technology that allows remote acquisition of objective study outcomes in a continuous and quantitative manner, which has been a challenge for classical clinical trials as we know them. Despite these challenges, the authors believe that the field will be advancing steadily toward to the ultimate goal of changing the course of these disorders and finding a cure. Our collective accomplishments to date within the relatively short time from the initial descriptions of RBD in 1986 are a testament to this view.

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RBD: Future Directions in Research and Clinical Care and Counseling

45

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45.1 Introduction

At the conclusion of this textbook on RBD, which comprises a compendium of all the major topics on RBD, the authors in this final chapter outline an array of future directions for RBD research and clinical care and counseling.

In the first section, entitled "RBD As a Critical Indicator in the 'Parkinson Pandemic': A Call to Action," the rationale for the compelling need for increased funding for research centered on RBD diagnosis, and further development of biomarkers and neuroprotective agents is given. In the section on "Future Epidemiological Research on RBD: Automatic Analysis and New Tools?" current

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and upcoming technologies which already have a place in the diagnosis of RBD, or are under development, are discussed. In the section "Polysomnography Is a Biomarker of Neurodegeneration and Not Only a Diagnostic Tool in RBD," the value of video, EMG, EEG, and their current development are discussed.

The concept of "prodromal RBD" is then presented, and its specific expected implications for research are explained. In the section "Idiopathic RBD, Cryptogenic RBD, or Isolated RBD," the rationale for the new term "isolated RBD" is given. Another section is devoted to "Recommendations of the International RBD Study Group for Clinical Disease-Modifying Trials" and presents how the advances in RBD research are reflected in updated recommendations. In the final section "The International RBD Study Group 2017 Prague Program Highlights and 'Hot Topics'," the current lines of research of the iRBD-SG are presented and selected highlights discussed. In the section on "Clinical Care Issues and Counseling," the difficult topic of how to talk to an affected patient and his family regarding the diagnosis and prognosis of RBD is discussed.

45.2 RBD as a Critical Indicator in the "Parkinson Pandemic": A Call to Action

In a recent viewpoint article in *JAMA Neurology* entitled "The Parkinson Pandemic – A Call to Action," Dorsey and Bloem report on how neurological disorders are now the leading worldwide cause of disability, with Parkinson's disease (PD) being the fastest-growing neurological disorder [1]. They state that "if PD were an infectious condition, it would rightly be called a pandemic" and issue a "call to action" to (1) prevent transmission or onset, (2) increase access to care, and (3) increase research funding. There is strong evidence that RBD is a critical indicator in the Parkinson pandemic in two ways, as early herald of future PD and as marker of increased global morbidity and disease burden in PD [2]. A "call to action" has already been initiated along several RBD-PD research fronts, prompted by how the emergence of excessive muscle tone during REM sleep reflects the damage done by the PD α-synuclein pathology to the pontine and medullary centers and pathways regulating REM sleep muscle tone [2]. Since >80% of idiopathic RBD (iRBD) patients will eventually develop PD or other synucleinopathy, with a mean latency of >10 years after iRBD onset [2], iRBD is a strong early indicator of future PD/Dementia with Lewy Bodies (DLB). This has triggered a strong call to action for early intervention to prevent or slow down the progression to PD/DLB. To that end, a consensus statement was published by the International Rapid Eye Movement Sleep Behavior Disorder Study Group (iRBD-SG) on devising studies for neuroprotection against PD/DLB in iRBD patients, who are considered ideal candidates for neuroprotective studies [3]. (This topic is discussed in Chaps. 3 and 44)

Neuroprotection is an urgent topic with a commensurate need to increase funding for research on developing neuroprotective agents that could be tested in iRBD patients. This research need is magnified by the second critical indicator of RBD, as marker of increased global morbidity and disease burden in PD [2]. There is more widespread morbidity in PD with RBD, with greater motor, cognitive, autonomic, and psychiatric dysfunction, and greater disease burden, compared to PD without

RBD [2]. So effective early intervention with neuroprotection in iRBD would not only slow down or halt progression to clinically manifest PD but also stave off the more severe form of PD associated with RBD.

Given that RBD is the premier biomarker of emerging PD, beginning at the time of iRBD diagnosis, efforts can be initiated to maximize the level of long-term functioning and minimize disease burden, as recently proposed from the field of physical medicine and rehabilitation [4]. As stated by the authors of this report, "the early involvement of rehabilitation and/or development of home exercise plans may aid in prolonging and even increasing function, independence, and quality of life, should [PD, DLB] neurodegenerative disorders develop later in life." Specific early interventions were put forward, beginning at the time of iRBD diagnosis (which we believe should also be offered to all RBD patients). These interventions were based on "the known sensorimotor impairments and functional limitations that progressively develop with Parkinson's disease and other synucleinopathies" [4]. Table 45.1 lists the key goals and techniques of physical therapy and occupational therapy (to which we added therapy of voice and speech impairments in iRBD) [5]. As stated by the authors, "the overarching objective of each of the above-mentioned interventions is to maintain motor function and quality of life [4]." Early tailored home exercise plans and group exercise activities can be developed and implemented. These would include cardiorespiratory and aerobic conditioning, enhanced balance with fall prevention, agility and mobility training, and awareness of posture. Also, a recent study found that regular sports activity in the elderly may have beneficial effects on prodromal PD markers, including RBD [6].

From the field of epidemiology comes the recent call to focus intensive research efforts on RBD as an early prodromal PD disorder [7]. Such research "presents an unprecedented opportunity to dissect the etiology of PD. Using PD prodromal

Table 45.1 Physical therapy and occupational therapy: early interventions in RBD[a]

(I) Physical therapy
1. Progressive strengthening and stretching of postural musculature
2. Trunk range of motion exercises: extension and rotation; dynamic reactive balance training
3. Large and big movements practice, to maximize movement amplitude and speed
4. Balance training for fall prevention
5. Agility training, to maintain mobility under challenging environmental/dual task conditions
6. Aerobic exercise to maintain cardiovascular fitness, cognitive fitness, and maximal level of function
7. Assessment and treatment of any gait deviations linked with RBD
(II) Occupational therapy
1. Securing the safety of the sleeping environment in RBD
2. Awareness of autonomic dysfunction, if present, and development of compensatory measures, for constipation, bladder dyscontrol, orthostatic hypotension
3. Cognitive rehabilitation for memory/cognitive dysfunction
4. Voice and speech therapy, for impairments involving aperiodicity, alternating motion irregularities, articulatory decay, and dysfluency

[a]Adapted in part from the text of reference [4]

symptoms as intermediate phenotypes, we may be able to identify factors that contribute to the development of these symptoms and factors that modify their progression to clinical PD." This line of research would also enable investigation of novel etiological hypotheses of PD/RBD development such as the (gut and nasal) microbiome and prion hypotheses [8–11].

45.3 Future Epidemiological Research in RBD: Automatic Analysis and New Tools?

Future epidemiological research on RBD should incorporate RBD research methods in much more detail than has been done in the past. Most epidemiological studies on RRD have been based on questionnaires only and therefore have assessed probable RBD [12], as discussed in Chap. 19, and only a few have incorporated polysomnography (PSG) in subgroups of patients [13, 14] or in a population-based study [15]. While it should be emphasized that the existence of large epidemiological studies with full PSG providing prevalence data on clinically isolated RBD or even prodromal RBD is of high importance to understand the true prevalence [12], it still needs to be said that all the published epidemiological cohorts to date have had limited numbers of participants and either no follow-up or only a limited number of follow-ups. For PSG analysis in epidemiological studies, the visual and the manual methods of counting tonic and phasic EMG activity are cumbersome, and detailed visual video analysis [16–20] has not been performed in larger studies up to now [12].

Therefore, recent instruments to automatically detect and quantify REM without atonia (RWA), such as the REM atonia index based on the chin EMG only [21–24], or the SINBAR method with tonic, phasic and any percentages for mentalis muscle [25] the computerized full SINBAR analysis method based on a combination of chin and upper extremity EMG quantification [26, 27], as discussed in Chap. 31, and other methods in development are very promising and with high potential for future use in epidemiological studies to detect RBD. Some of these automatic methods have already been applied in RBD epidemiology, such as the computerized quantification also used for the SINBAR method [27]. Future efforts should evaluate whether recording of chin and upper extremity EMGs alone, is suitable even in the absence of a full PSG, or with a minimum to-be-determined combination of selected other channels, e.g., EOG, single-channel EEG, or oximetry, just to mention a few potential candidates.

Video recording, as the other major component of video-PSG, has only been investigated in detail by a few groups [16–19, 28–30] and in limited cohorts of iRBD patients. The first epidemiological studies on RBD that incorporated full PSG in a subset of their patients did not include video analysis at all [13–15]. However, despite being cumbersome and highly time-consuming, this type of video analysis is currently being used in the first double-blind, placebo-controlled study of RBD in DLB [31]. For practical clinical purposes, a quick RBD severity scale based on PSG–EMG artifacts and video has been developed [32].Whether automatic video analysis tools, perhaps even as a stand-alone technique, will provide another independent access to epidemiological RBD research, remains to be shown in the future.

Apart from incorporating RBD into large and carefully designed epidemiological studies, another important advancement for the early detection of RBD in the general population could lie within the "big data" generated from the growing community of body-tracking individuals using their smartphones and other gadgets, alone or in combination with several other technologies. Other screening methods, e.g., actigraphy, have shown their potential in detecting RBD [33]. Any future epidemiological study in RBD will need to satisfy high-quality criteria for diagnosis [12, 34].

Besides video-PSG providing quantitative data on the progression from normality to prodromal RBD, to clinically isolated RBD, and then to overt alpha synuclein disease, details of this progression still need to be elucidated, e.g., in the different manifestations (video or tonic/phasic/any EMG) [12, 35, 36, 38, 39].

Although much progress has been made with multiple additional biomarkers of alpha synuclein-related neurodegeneration [12], as discussed in Chap. 36, their strengths, weaknesses, and suitability to predict imminent conversion, or conversion to a specific endpoint (e.g., DLB) have not been fully elucidated and need further investigation, despite promising initial results [12, 36, 38].

45.4 Polysomnography Is a Biomarker of Neurodegeneration and Not Only a Diagnostic Tool in RBD

Among the multiple biomarkers of neurodegeneration investigated in isolated RBD, video-polysomnography itself should be seen as a biomarker of neurodegeneration [12], apart from its currently obligatory role in the diagnosis of iRBD. Video-PSG can indeed provide "quantifiable and potentially treatment-responsive biomarkers of neurodegeneration" [12], but also is able to capture prodromal RBD.

45.5 The Concept of Prodromal RBD

The concept of prodromal RBD [12, 28, 29] has recently been introduced based on several PSG studies focused on EMG and video [12, 27, 28, 37–39]. Criteria have been developed that clearly delineate prodromal RBD from normality on the one side and the fully evolved state of clinically isolated RBD (formerly called idiopathic RBD) on the other side (Fig. 45.1).

This allows for a clearly defined four-step continuum from normality to prodromal RBD, to isolated RBD, and then to overt clinical alpha synuclein disease that reflects the insidious onset of both RBD and alpha synucleinopathy diseases [12]. This concept will also need to be explored in further studies and may prove useful in at least two major regards:

1. The concept of prodromal RBD helps to clearly delineate the onset of a clinically isolated RBD phase, and acknowledges that there is an insidious onset of RBD, with a prodromal phase (formerly called subclinical RBD [12, 37]). This is impor-

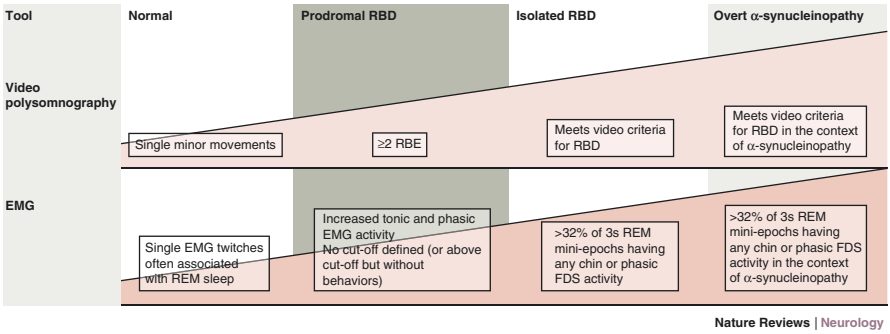

Fig. 45.1 The concept of prodromal RBD within the continuum from normality to overt alpha synuclein disease

tant, because not only is the end of the RBD phase (i.e., conversion to overt neurodegenerative disease) clearly delineated but also its beginning manifestation of fully developed RBD, "(clinically) isolated RBD" [12].

2. A stable and identifiable stage of prodromal RBD could even open a window into the detection of incipient neurodegeneration at a much earlier stage and thus a potentially earlier treatable stage. This is important, since as previously discussed within the earlier concept of "subclinical RBD," we can predict that some patients will progress directly from prodromal RBD to overt synucleinopathy, without demonstrating the more typical intermediate step of clinical RBD [37].

45.6 Idiopathic RBD, Cryptogenic RBD, or Isolated RBD?

Based on the fact that the original term of idiopathic (iRBD) has been increasingly shown to be imprecise based on the very high progression rate to alpha synuclein disease, and other abnormal findings beyond RBD [38, 39], and based on the fact that the subsequently proposed term cryptogenic RBD can also no longer be sustained in light of the overwhelming clinical, imaging, tissue and fluid, and autopsy evidence of alpha synuclein pathology in formerly idiopathic or cryptogenic RBD, Högl, Stefani, and Videnovic have proposed the term "(clinically) isolated RBD," a more updated and accurate depiction of "iRBD" [12]. This also has a secondary advantage of maintaining the abbreviation of iRBD.

45.7 Recommendations of the International RBD Study Group for RBD Clinical Trials

This important topic is covered in detail in Chap. 44, and briefly in Chap. 3. The International RBD Study Group (IRBD-SG) first published a consensus paper on how to devise controlled active treatment studies with symptomatic

and neuroprotective therapies in isolated RBD, based on a 2-day meeting of the IRBD-SG in Germany [3]. In that manuscript, the authors tried to develop a first consensus to identify essential methodological components for randomized trials in RBD, including potential screening and diagnostic criteria, inclusion and exclusion criteria, automatic and visual scoring methods, etc. Nevertheless, the clinical global index (CGI) was proposed as the first and primary endpoint for RBD treatment trials in this first consensus paper, mainly because at that time it was considered cumbersome and difficult to perform vPSG on all patients.

In the light of increasing evidence of problems with use of questionnaires alone [12, 34], as discussed in Chap. 19, and the multiple inherent limitations of the CGI for the assessment of unconscious behaviors that are often missed by the partner due to the partner being asleep and the RBD behaviors occurring in the dark, the CGI must now be considered to be too vague and probably also open to too many confounders and bias [3, 12].

With regard to the video-PSG, at that time, the consensus was that quantifying changes in REM atonia and REM sleep phasic motor activity with therapy was highly desired but was considered impractical to achieve by the considerable cost and cumbersomeness [3]; therefore a recommendation was made that only a separate arm of any future RBD trial at a specialized center should perform this analysis [3]. Also at that time, night-to-night variability of behaviors was considered to be a potential confounder, but recent studies have shown that the degree of RWA shows much less night-to-night variability [21, 40]. Also, isolated minor, and multiple minor, elementary jerks seen on the video are much more reliable and stable findings both inter- and intraindividually across nights, in contrast to outbreaks of complex and violent behaviors [12, 17].

It is fortunate that due to the contributions of multiple active research groups from different continents, the field has evolved further since this first consensus report published in 2013 [3] (that was based on a IRBD-SG meeting that took place in 2011). Therefore, the authors are confident that there is sufficient current consensus to state that PSG is not only mandatory in the diagnosis of RBD but also as a study endpoint, and future research will show whether even PSG can be replaced by other methods (e.g., brain imaging) or other assessments of movements and behaviors during the night as study endpoints.

45.8 IRBD-SG 2017 Prague Program Highlights and "Hot Topics"

The annual meetings of the iRBD-SG (see Chap. 3) assemble progress in RBD clinical and basic science research. The following summarizes the current RBD "state of the art," based on the October 12–13, 2017 meeting of the iRBD-SG in Prague, Czech Republic. Table 45.2 contains the program with its topics and presenters.

Table 45.2 Program of the 11th Annual International REM Sleep Behavior Disorder Study Group Meeting, Prague, Czech Republic, October 12–13, 2017

Technical innovation		
Electrophysiology	Soria-Frisch A, Castellano M, Ibanez D, Kroupi E, Montplaisir J, Gagnon JF, Postuma R, Oertel W, Ruffini G	Machine learning decision support system for alpha synucleinopathies prognosis and diagnosis based on EEG
	Jennum P	Electromyographic pattern in RBD—validation of available methods
	Espinoza D, Corodova T, Diaz J, Bassi A, Vivaldi EA, Ocampo-Garces	Envelope analysis of electromyogram in REM sleep behavior disorder patients
	Arnulf I	Sleep talking in RBD
New technology	Arora S, Barber T, Lo C, Rolinski M, Lawton M, Baig F, Ruffmann C, Oertel WH, Quinell T, Denis G, Zaiwalla Z, Shlomo YB, Little M, Hu M	The use of wearable technology to delineate and stratify RBD
	Stefani A, Högl B	Screening for idiopathic RBD: a multimodal low-cost approach (actigraphy)
	Rusz J	Speech analysis reveals prodromal markers of neurodegeneration in RBD
Imaging	Miyamoto M, Miyamoto T	The prospective study of nigrostriatal dopaminergic function using FMT-PET in idiopathic REM sleep behavior disorder
	Arnaldi D, Morbelli S, Nobili F	Usefulness of DAT SPECT as a stratification biomarker for neuroprotective trials: where are we?
	Meles S, Janzen A, Mayer G Luster M, Booij J, Leenders KL, Oertel WH	Fluoro-desoxy-glucose PET in RBD and PD
	Dusek P	Multimodality imaging of neurodegeneration in RBD
	Gagnon JF	Changes in cortical and subcortical gray matter linked to cognitive impairment and motor deficits in RBD
	Fantini ML, Beal C, Sescousse G, Chassain C, Ulla M, Marques A, Vitello N, Pereira B, Durif F	Abnormal activity of the reward system in RBD: an fMRI study
Biomarkers		
Genetics	Gan-Or Z	Genetics of RBD and conversion to synucleinopathies
	Budkov, J, Bendova Z, Koprivova J, Bartos A, Sonka K	Circadian rhythms of melatonin and clock gene expression in idiopathic RBD

Table 45.2 (continued)

Biomaterial	Antelmi E, Plazzi G	Skin biopsy and p-α synuclein deposits in iRBD: update
	Heintz-Buschart A, Mollenhauer B, Janzen A, Mayer G, Trenkwalder C, Oertel WH, Wilmes P	Microbiome analysis in stool of RBD versus PD versus healthy controls—a pilot study
Clinical features	Iranzo A	Excessive daytime sleepiness as a maker of synucleinopathy in iRBD
	St. Louis EK, Boeve AR, Timm P, McCarter SJ, Sandness D, Silber MH, Boeve BF	Neurodegenerative biomarkers frequency in idiopathic REM sleep behavior disorder at baseline in the Mayo Clinic prospective RBD registry
	Nisser J, Derlien S, Bulak P, Schwab M, Witte OW, Smolenski U, Schultze T, Rupprecht S	Mild motor abnormalities in "idiopathic" REM sleep behavior disorder: a diagnostic window to early neurodegeneration
	Schenck CH	RBD screening and treatment outcome questionnaires should include the bed partner
	Sasai-Sakuma T, Takeuchi N, Inoue Y	Gender differences in clinical symptoms and polysomnographic variables in RBD
	St. Louis EK, Boeve AR, Timm P, McCarter SJ, Sandness D, Silber MH, Boeve BF	Phenoconversion to synucleinopathy in women with REM sleep behavior disorder
	Miyamoto M, Miyamoto T	Lewy body disease status in idiopathic REM sleep behavior disorder: an observational cohort study
	Ruzicka E	Tiny disturbance of eye movements is linked to an executive dysfunction in RBD
Basic research to clinical trials		
Basic research	Peever J	Circuit mechanisms of REM sleep in RBD
	Luppi PH	Genetic rat models of RBD obtained by inactivating glutamate or GABA/glycine neurons
RBD in other diseases	Heidbreder A	RBD in IgLON-5 disease
	Mayer G, Rodenbeck A, Kesper K	Dose-dependent suppression of muscle tone in REM and NREM sleep by sodium oxybate in patients with narcolepsy
	Partinen M, Ylkoski A	Symptoms of RBD in patients with PD related to mortality in a cohort of PD patients. A 4-year prospective follow-up study
	Wing YK	Depression and RBD: an update

(continued)

Table 45.2 (continued)

Treatment	Inoue Y, Matsui K, Sasai-Sakuma T	Yokukansan (Yi-Gan San) treatment on rapid eye movement sleep behavior disorder: results from 42 patients
Clinical Trials	Boeve B, Yo-El J	Neuroprotective treatment trial planning in REM sleep behavior disorder: the NAPS consortium and protocol
Common project of the iRBD-SG	Postuma R	Outcome in RBD, international data collection

45.9 The IRBD-SG 2017 "Hot Topics"

45.9.1 Improved Assessment and Diagnosis Through Technical Innovation

The application of new technologies, e.g., machine learning for the analysis of EEG patterns in RBD patients, appears to be one promising research route. The introduction of such technical innovations promises the opportunity to even distinguish among the different directions of neurodegeneration (e.g., PD vs. DLB vs. MSA) at an early stage because it allows observing disease-specific changes in the EEG patterns.

Speech has also been identified as a potentially very sensitive marker and thus an important indicator for abnormal motor function and movement coordination as early changes due to prodromal neurodegeneration. A quantitative analysis of speech recordings allows evaluating deviant speech dimensions connected with phonation, articulation, and prosody. This has been already demonstrated in a significant correlation of motor speech dysfunction in idiopathic RBD patients [5]. Against this background, advanced speech analysis could be used as a longitudinal progression marker that is easy to apply and easy to access, although language-specific applications are necessary.

Actigraphy recordings, as an easy-to-apply gadget, can disclose typical patterns of sleep disruption in RBD patients and could be a useful instrument for screening for RBD [33]. Other wearable tools, for instance, integration into mobile phones, can enable the patient to monitor motoric changes and can collect detailed data on the progression of motoric changes—as well as the normalization of motor activity with therapeutic intervention.

These and further (large) data collection tools, when combined with machine learning approaches, could have a high potential for diagnostics because they convey substantially more information to identify the typical patterns among the different alpha synucleinopathies.

Beside this, automatic analysis of EMG activity during PSG recordings could offer a useful tool not only to save time but also to find distinctive EMG patterns in RBD patients. A harmonization of derivation and montages is needed to achieve comparable data.

45.9.2 Improved Diagnosis from Biomarkers

The development of "dynamic" biomarkers is a promising RBD research avenue. Biomarkers of RBD that are highly desirable and much needed are those with the ability to stratify who, when, and to which entity phenoconversion occurs from idiopathic RBD to overt synucleinopathy. The systematic and unified collection of biospecimens for studies of genetic and epigenetic influences promises to elucidate risk factors but also protective factors, including data from nonconverters who have RBD but do not convert during their lifetimes. The "big data" genetic analysis can thus contribute to personalized therapies—"precision medicine"—as described in Chaps. 41 and 44. To ensure a comprehensive data collection that can fulfill the diagnostic ambitions, biomaterial should not be confined to blood or cerebrospinal fluid. Beyond these standard specimens, collection of skin biopsies to detect alpha synuclein deposits of different body parts has shown compelling results [41, 42]. Another promising biomarker is nasal and gut microbiome in RBD patients [9]. Based on these findings, the list of biomarkers on which data should be collected ought to be developed.

The utilization of new ideas in the development of biomarkers in combination with high standard diagnostic tools, e.g., brain imaging, and also utilization of advances in interpretation and techniques are promising avenues that current research is focusing on [41–44].

Table 45.2 outlines the agenda of the iRBD-SG scientific meeting in October 2017 and thus an overview of the topics discussed. As the titles indicate, the diagnostic relevance of RBD and the innovation of diagnostic tools—both through more effective use of technology and more systematic and informed data collection—were the most discussed topics. Further, the need for harmonized assessments/standardized protocols to answer questions concerning phenoconversion, along with epidemiology, and recognition of demographic changes and gender differences and comorbidities were discussed.

Another research area in RBD that needs to be further developed, and which has been presented at previous iRBD-SG meetings by K-Y Jung, concerns EEG and evoked potential (EP) studies of iRBD, which provide another perspective on brain dysfunction in iRBD. Jung and his group have published three studies to date on this topic [45–47]. The first (EP) study found reduced P300 amplitude during a visuospatial attention task in the iRBD patients, implying cortical dysfunction in iRBD [45]. The second study analyzed beta frequency range EEG during sleep and found increased corticomuscular coherence during REM sleep in patients with iRBD [46]. The third study found altered functional EEG connectivity in iRBD patients, indicating altered functional EEG networks in iRBD [47]. Finally, from a topographic or neural network viewpoint, it is unclear why patients with RBD show locomotor behavior, e.g., make running movements, while they remain in a recumbent position, and only rarely while upright with a fully erect spine.

45.10 Clinical Care Issues and Counseling

Standards should be developed for the management of patients with isolated RBD (iRBD), apart from the treatment of injurious dream-enacting behaviors, since iRBD patients 50 years and older are at high risk for future parkinsonism. The topic of when and what to tell the patients and spouses about this high risk, and the need for follow-up, has been addressed in Chap. 22 and also in a recent publication [48]. The authors of this article state that "the consensus is to generally disclose the neurodegenerative risk to patients (with the caveat that phenoconversion and its temporal course remain uncertain in individuals without "soft neurodegenerative signs" and those under 50 years of age)", to suggest a healthy lifestyle and to take part in prospective cohort studies in anticipation of eventual neuroprotective trials." The first part of this chapter, drawing from a recent and highly pertinent article from the physical medicine and rehabilitation literature [4], described the initiation of physical and occupational therapy routines to be recommended at the time of iRBD diagnosis. Also, the sleep physician needs to consider educational, cultural, religious, and other factors. Furthermore, pertinent information on PD, DLB, and MSA should be made available to newly diagnosed RBD patients and their spouses, since many patients will ask their sleep medicine doctor, "What is Parkinson's disease?" It is important for RBD patients and their spouses to be accurately informed about these neurological disorders that are likely to emerge in the future and to have them understand the cardinal signs and symptoms and longitudinal course. An excellent description of the typical symptoms of these neurodegenerative disorders can be found in the following web pages:

http://www.parkinson.org/understanding-parkinsons/what-is-parkinsons
https://www.lbda.org/content/10-things-you-should-know-about-lbd
https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Multiple-System-Atrophy

The majority of patients with iRBD feel otherwise healthy, without motor or cognitive complaints, and it is very difficult to anticipate when parkinsonism or cognitive impairment will first appear. It is reasonable to inform patients that, if certain symptoms arise, such as motor slowness or memory problems, they should ask for neurological consultation. It is important to make patients understand that the development of a neurodegenerative disease is never an abrupt event and that most likely there will be enough time to diagnose it and initiate the appropriate treatment if necessary.

Doctors following patients with iRBD should be aware that parkinsonism and dementia might evolve with time and should understand how these symptoms manifest. Most patients with iRBD who develop Parkinson's disease do not have resting tremor initially but rather may have complaints of motor slowness and shuffling gait with short steps, and subsequently facial akinesia, hypophonia, and reduced arm swing will appear, followed by rigidity and akinesia. In DLB, the onset of dementia is typically preceded by a long period of mild cognitive impairment (MCI), during which

time memory problems are usually the main complaint. The neuropsychological manifestations of MCI in the setting of iRBD are similar to those of DLB, although less severe; MCI is characterized by executive, visuospatial, and memory dysfunction. If dementia occurs, it is often later and accompanied by akinetic-rigid parkinsonism, visual hallucinations, fluctuating cognition and alertness, and delusions of poverty and jealousy. The presence of atypical parkinsonism or gait problems, nocturnal stridor, or symptomatic orthostatic hypotension may suggest the diagnosis of multiple system atrophy.

For clinical care, furthermore, a method to reliably measure and monitor the severity of RBD symptoms over time should be developed. The development of RBD support groups has been advocated by patients with RBD, and so this promising patient-centered idea should be promoted in various ways by members of the RBD clinical and research community, in collaboration with interested RBD patients.

Conclusions

Since the first formal description of RBD in humans in 1986 by Carlos H. Schenck, Mark W. Mahowald, and colleagues three decades ago [49], rapid and dynamic clinical and research developments have taken place, and at present there is a highly active and productive international research involvement with RBD, spearheaded by the iRBD-SG. Nearly all authors of this comprehensive textbook on RBD are members of the iRBD-SG, which is ideally positioned to further develop and advance the research field, and help answer important open questions presented in this RBD compendium, as well as to respond to the needs of clinical care physicians and their patients. Finally, the RBD research field welcomes investigators from diverse clinical and basic science disciplines who can contribute innovative new techniques and research strategies to help accelerate critical advancements.

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