ELSEVIER

Sleep Medicine 10 (2009) 174–181

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original Article

The relation between abnormal behaviors and REM sleep microstructure in patients with REM sleep behavior disorder

Birgit Frauscher [a], Viola Gschliesser [a], Elisabeth Brandauer [a], Hanno Ulmer [b], Werner Poewe [a], Birgit Högl [a,*]

[a] *Innsbruck Medical University, Department of Neurology, Anichstrasse 35, A-6020 Innsbruck, Austria*
[b] *Innsbruck Medical University, Department of Statistics, Informatics and Health Economics, Innsbruck, Austria*

Received 17 September 2007; received in revised form 14 December 2007; accepted 15 January 2008
Available online 24 March 2008

Abstract

Objective: To investigate the temporal relation between rapid eye movement (REM) sleep microstructure (REMs, EMG activity) and motor events in REM sleep behavior disorder (RBD).
Methods: Polysomnographic records of eight patients with RBD were analyzed and compared with those of eight sex- and age-matched controls. We examined sleep microstructure for REM sleep with and without REMs and phasic chin EMG activity and their temporal relation to motor events on video.
Results: All types of motor events were either more frequent in RBD patients than in controls ($P \leqslant 0.007$) or present solely in RBD patients. In RBD, major motor events were significantly more frequent during REM sleep with REMs than during REM sleep without REMs (violent, 84.0% vs. 16.0%, $P < 0.001$; complex/scenic behavior, 78.1% vs. 23.2%, $P < 0.001$; major jerks, 77.5% vs. 20.3%, $P < 0.001$), whereas minor motor activity was evenly distributed (54.1% vs. 45.9%, $P = 0.889$). Controls showed predominantly minor motor activity with rare myoclonic body jerks. The distribution of motor events did not differ between REM sleep with and without REMs (40.9% vs. 59.1%, $P = 0.262$).
Conclusions: In RBD, major motor activity is closely associated with REM sleep with REMs, whereas minor jerks occur throughout REM sleep. This finding further supports the concept of a dual nature of REM sleep with REMs and REM sleep without REMs and implies a potential gate control mechanism of REM sleep with REMs for the manifestation of elaborate or violent behaviors in RBD.

Keywords: REM sleep behavior disorder; REM sleep microstructure; EMG activity; Rapid eye movements; Video analysis

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia of REM sleep characterized by a history of injurious or disruptive dream-enacting behaviors such as talking, yelling, grabbing, arm flailing, punching or jumping out of bed [1]. The muscle atonia normally prevailing during REM sleep is lost, and excessive phasic or tonic EMG activity is found in the polysomnographic registration [2]. Phasic EMG activity is characterized by short-lasting muscle twitches, whereas tonic EMG activity shows a sustained elevated muscle tone in the EMG registration.

REM sleep can be subdivided into REM sleep with REMs and REM sleep without REMs. Since the early work of Jouvet and coworkers, two motor systems modulating motor activity during REM sleep have been proposed: one for generating muscle atonia and one for

* Corresponding author. Tel.: +43 512 504 23811; fax: +43 512 504 23842.
E-mail address: birgit.ho@i-med.ac.at (B. Högl).

1389-9457/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2008.01.003

suppressing locomotor activity [3]. Recently, REM sleep with REMs was shown to act as a functionally isolated and closed intrinsic loop, whereas REM sleep without REMs was found to be identical to a state with reduced alertness, suggesting two distinct functions of these two components of REM sleep [4].

Previous polysomnographic studies in RBD have focused on characterization of EMG motor activity in RBD [5–8]. A scoring method differentiating between tonic and phasic EMG activity in RBD patients was proposed in 1992 [5] and replicated in a larger sample of 23 patients in 2005 [6]. A slightly different approach has been undertaken by differentiation between short- and long-lasting muscle activity [7]. Focusing on phasic EMG patterns, a recent study sampled phasic EMG activity of the chin, legs and arms in both REM sleep and non-REM sleep in order to determine a phasic electromyographic metric [8].

A few studies have also incorporated video results in the analysis of RBD, applying a basic categorical analysis of simple vs. complex movements [9,10] or mild, moderate, or severe RBD intensity [11]. In RBD due to Parkinson's disease, restoration of normal muscle control was observed during REM sleep [12]. Recently, our group performed a detailed video analysis in RBD patients. We demonstrated that patients with symptomatic RBD exhibited a very high number and a large variety of motor events during REM sleep in comparison to healthy controls. However, most motor events were minor, and violent episodes accounted for only a small fraction, even in severe RBD [13].

Based on our clinical observations, which suggest a close temporal relationship among the presence of REMs, bursts of phasic muscle activity and videographic motor events in patients with RBD, we sought to investigate this relationship in detail, specifically among REM sleep with REMs, phasic EMG activity and motor events in patients with RBD as compared to healthy controls.

2. Methods

2.1. Patients and controls

Files of patients undergoing routine polysomnography at the neurological sleep laboratory of Innsbruck Medical University (Austria) were screened for the diagnosis of either idiopathic or symptomatic RBD according to ICSD-2 criteria [2]. Inclusion criteria were severe RBD and at least 5% of stage REM sleep during sleep period time. Severe RBD was defined as the occurrence of gross movements during polysomnography such as waving the arms vigorously, kicking, punching, sitting up, jumping out of bed, talking loudly, or shouting [11]. Exclusion criteria were technical reasons (e.g., EOG artifacts, video quality) or clinically relevant sleep-related breathing disorders with a respiratory distress index >20/h, which could potentially interfere with the scoring of the EMG activity in the chin muscles.

A sex- and age-matched control group was established based on patients without RBD, who were examined for suspected sleep-related breathing disorders. Patients were eligible for inclusion in the control group if a sleep-related breathing disorder was excluded by PSG (a diagnosis of primary snoring was not considered as exclusion criterion) and if they had no further history or polysomnographic manifestation of a sleep disorder (e.g. restless legs syndrome, periodic limb movement disorder).

2.2. Polysomnography

Polysomnography was performed with a digital polygraph (Brainlab version 4.0, Schwarzer Inc., Munich, Germany) and consisted of vertical and horizontal electrooculography (ROC-A1, LOC-A1, supraorbital–infraorbital, infraorbital–supraorbital), electroencephalography (C3-A2, C4-A1, O1-A2, O2-A1), electrocardiography, electromyography of the mental, submental, right and left tibialis anterior muscles, nasal air flow (thermocouple), thoracal and abdominal respiratory effort, oxygen saturation and tracheal microphone. Digital video was recorded with an infrared camera (Elbex Inc., EX series, Regensburg, Germany) and processed using a sampling (data) rate of 1.5 Mbits/s. Screen resolution for video analysis was 1280×960 pixels. For scoring REMs, EOG was recorded with the low-frequency filter at 0.04 Hz, the high-frequency filter at 35 Hz, a sampling rate of 125 Hz and amplification set at 200 μV per mm. For scoring chin EMG activity, bipolar surface EMG was recorded with the low-frequency filter at 50 Hz, the high-frequency filter at 300 Hz, a sampling rate of 500 Hz, and amplification set at 5 μV per mm. Impedance of surface EMG electrodes had to be lower than 10 kΩ.

Sleep stages were scored according to the criteria of Rechtschaffen and Kales [14] with allowance for scoring REM sleep despite persistence of tonic or phasic muscle activity [15]. In patients and controls, the occurrence of the first rapid eye movement in the electrooculographic channel was used to determine the onset of a REM sleep period. The end of a REM sleep period was determined either when no rapid eye movements were detected for three consecutive minutes, when the patient awakened, or when K complexes or spindles were observed [16]. Night 1 was considered an adaptation night.

2.3. Analysis of REM sleep microstructure and video analysis

To better examine the relation between REMs and motor events, we proceeded as follows.

2.3.1. Coding of tonic and phasic EMG activity during REM sleep

Tonic and phasic EMG activity was scored separately as suggested by Lapierre and Montplaisir [5]. Phasic EMG activity was scored from the mental and submental EMG recordings as the percentage of 3-s mini-epochs containing phasic EMG events. Phasic EMG events were defined as any burst of EMG activity lasting 0.1–5 s with an amplitude exceeding four times the background EMG activity during REM sleep. Tonic REM has been defined as the presence of tonic mental or submental EMG activity of at least 50% of the 30-s REM epoch. REM atonia has been defined as the percentage of 30-s REM epochs with less than 50% tonic EMG activity. EMG activity was clearly distinguished from EMG increases on the basis of respiratory arousals or snoring artifacts.

2.3.2. Coding of REM sleep with and without REMs

REMs were defined as 90° out-of-phase deflections in either horizontal or vertical EOG channels of any amplitude. Mini-epochs containing at least one REM were scored as REM sleep with REMs (also known as "phasic" REM sleep), whereas mini-epochs without REMs were scored as REM sleep without REMs (also known as "tonic" REM sleep). Moreover, REM density (percentage of 3-s mini-epochs with at least one REM per total number of 3-s mini-epochs) was also calculated. Note that repetitive REMs per mini-epoch did not contribute to a higher REM density.

2.3.3. Analysis of video events in relation to REMs and phasic EMG activity

After manually coding phasic EMG activity as well as REM sleep with REMs and REM sleep without REMs, the video recordings were carefully searched for motor events by one of the authors (B.F.) with respect to background REM microstructure (REMs, phasic EMG activity). Video analysis was performed on an additional computer screen set up beside the monitor showing the polysomnogram. All video recordings were digitally synchronized with the PSG recording (video PSG signal synchronization, ±200 ms) to allow correlation of the video recording with REM sleep microstructure. For this study, a classification system of motor behaviors in RBD validated and recently published by our group was used. Mean interscorer agreement was 0.91 ($P < 0.001$) [13]. Classification of motor events was supervised by a senior neurologist specialized in movement disorders and sleep (B.H.). The following motor events were differentiated: violent motor events, complex/scenic behaviors, major jerks or movements, and simple jerks/minor movements. For each motor event, one of the abovementioned categories was chosen. In the case of overlap, the more severe category was chosen (in ascending order: simple jerks/minor movements, major jerks or movements, complex/scenic behaviors, violent motor events). The classification of motor behaviors is given in Table 1. The presence or absence of motor events on the video and their classification were indicated per mini-epoch. The duration of complex/scenic and violent motor events was measured using a hand-held chronograph. The majority of events lasted longer than one mini-epoch. Moreover, all movement categories were stratified according to REM sleep with REMs and phasic EMG activity.

2.4. Statistics

SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL) was used for all statistical analyses. Descriptive statistics are given as means ± standard deviation or frequencies (percentages), as applicable. Due to the small sample size, differences between RBD patients and controls as

Table 1
Classification of video-recorded motor events

Types of motor events	Examples
Violent motor events Forceful and vehement movements that could potentially injure a bed partner	Kicking, punching, jumping out of bed, fighting
Scenic/complex behaviors Apparent "acting out" of dream contents or movements different from elementary simple events in terms of complexity of action	Laughing, crying, singing, gesturing, searching for something, chewing, smacking, grimacing, sitting up in bed, body rolling
Major jerk/movement Simple movements of great excursion of the body being mostly of myoclonic nature	Whole body jerk, gross body movement, raising the arm, isolated elevation of one leg
Minor motor activity Small jerky or non-jerky excursions that include one body part and usually would not be noticed by a sleeping bed partner.	Isolated finger twitches, small toe or foot movements, mouth openings

well as CNS drug naïve RBD patients vs. patients treated with CNS active medications were evaluated using the non-parametric Mann–Whitney-*U*-test. For all patients and controls, the mean number of motor events (violent motor events, complex/scenic behaviors, major jerks or movements, and simple jerks/minor movements) and their distribution (REM sleep with REMs, REM sleep without REMs; phasic EMG activity vs. no phasic EMG activity), as well as their initiation (REM sleep with REMs vs. REM sleep without REMs, phasic EMG activity vs. no phasic EMG activity) were examined for significant associations using the Wilcoxon test for paired data sets. Multiple comparisons for motor events were accounted for using Bonferroni correction. In this case, *P*-values <0.0125 (testing for four variables) or < 0.0167 (testing for three variables) were deemed to indicate statistical significance. In all other cases, a *P*-value <0.05 was considered significant.

3. Results

3.1. Demographics

Of 39 screened patients with RBD, eight (seven men, one woman) were selected according to inclusion and exclusion criteria. Four suffered from idiopathic and four from symptomatic RBD (two patients due to narcolepsy with cataplexy, one patient due to Parkinson's disease, one patient due to multiple system atrophy). Mean age was 56.3 ± 12.3 (range: 33–68) years. Four patients were treated with antidepressants (MAO inhibitor, $n = 1$; selective serotonin reuptake inhibitor, $n = 1$; tricyclic antidepressants, $n = 2$), and one patient additionally with levodopa. None of the four patients treated with central nervous system active drugs reported a relation between the onset of RBD and the initiation of central nervous system active treatment. Moreover, no clinical effect of various medications on RBD symptoms was observed.

Mean age of the controls (seven men, one woman) was 56.3 ± 12.3 (range: 33–68) years. None of the controls had a history of central nervous system active medication.

3.2. Polysomnographic results

Polysomnographic data on patients with RBD and controls are given in Table 2. In patients with RBD, analysis of REM sleep microstructure yielded a mean percentage of REM atonia of 46.6 ± 35.3%, and a mean phasic EMG activity of 41.7 ± 17.2%. In contrast, the control group exhibited a higher mean percentage of REM atonia (98.9 ± 1.5%; $P < 0.001$) and a lower mean percentage of phasic EMG activity (11.0 ± 5.8%; $P < 0.001$). No difference in REM density was seen between the two groups ($P = 0.065$). Further information on REM sleep in both groups is given in Table 3. No significant difference concerning REM sleep latency, number of REM episodes, total REM sleep duration, and REM sleep microstructure ($P > 0.05$) was seen between drug-naive RBD patients and RBD patients under central nervous system active medication.

3.3. Relation between abnormal movements during REM sleep and REM sleep microstructure (REMs, phasic EMG activity)

In patients with RBD, a mean of 2070 ± 1208 mini-epochs of REM sleep were registered. A mean of 24.1 ± 22.1 (1.7 ± 2.3%) mini-epochs contained violent motor events, 108.9 ± 37.8 (6.7 ± 4.0%) complex/scenic behaviors, 59.6 ± 39.1 (2.9 ± 1.3%) major jerks/movements, and 458.6 ± 222.9 (26.6 ± 14.8%) minor motor activity (small jerks/minor movements.

As compared to healthy controls, all types of motor events were either more frequent in RBD (major jerks/movements, $P = 0.007$; minor motor activity, $P = 0.001$) or present solely in the patient group (violent motor events, $P < 0.001$; complex/scenic behaviors, $P < 0.001$). For details see Table 3.

The mean frequencies of motor events in REM sleep with REMs vs. REM sleep without REMs are demonstrated for patients and controls in Table 4. In patients with RBD, a significant association between mini-epochs containing major motor events and REM sleep with REMs was shown following Bonferroni correction

Table 2
Polysomnographic variables in the RBD and the control group

	RBD patients, mean ± standard deviation	Controls, mean ± standard deviation	*P*-value*
Sleep period time (SPT)	463.9 ± 14.9	456.3 ± 14.7	0.279
Sleep efficiency (%)	85.4 ± 8.6	86.1 ± 7.9	0.878
Stage 1,2, % SPT	61.7 ± 7.5	58.1 ± 10.4	0.574
Stage 3–4, % SPT	2.8 ± 2.4	5.3 ± 5.2	0.382
Stage REM, % SPT	22.6 ± 13.2	17.5 ± 5.6	0.721
REM duration (min)	104.4 ± 60.9	78.3 ± 25.1	0.645
Sleep onset latency (S2) (min)	17.9 ± 143.4	18.0 ± 9.5	0.878
Respiratory distress index	5.2 ± 4.7	2.3 ± 1.7	0.234
Oxygen desaturation index	2.8 ± 2.4	0.8 ± 1.3	0.195

* *P*-values were calculated with the Mann–Whitney-*U*-test to compare patients with RBD versus control subjects.

Table 3
Analysis of REM sleep microstructure and video-polysomnographic findings in the RBD and the control group

	RBD patients, mean ± SD	Controls, mean ± SD	*P*-value*
REM sleep microstructure			
REM episodes (*n*)	3.1 ± 1.2	4.1 ± 1.1	0.13
3 s REM mini-epochs (*n*)	2070.3 ± 1207.8	1565.5 ± 501.1	0.645
REM density (%)	44.6 ± 14.8	32.1 ± 9.8	0.105
Phasic EMG activity (%)	41.7 ± 17.2	11.0 ± 5.8	0.001
REM atonia (%)	46.6 ± 35.3	98.9 ± 1.5	<0.001
Video-polysomnographic results			
Little jerks/minor movements	458.6 ± 222.9	22.8 ± 15.8	0.001
Major jerks/major movements	59.6 ± 39.1	5.0 ± 2.7	0.007
Scenic/complex behaviors	108.9 ± 37.8	0	<0.001
Violent motor events	24.1 ± 22.1	0	<0.001

* *P*-values were calculated with the Mann–Whitney-*U*-test to compare patients with RBD versus control subjects.

Table 4
Relation between motor events and REM sleep with REMs vs. REM sleep without REMs

Patients			
Mini epochs, mean ± SD	REM with REMs 931.1 ± 648.8	REM without REMs 1139.1 ± 635.5	*P*-value#
Violent motor events, mean ± SD	20.0 ± 17.1	4.1 ± 5.3	0.012*
Complex/scenic behavior, mean ± SD	84.3 ± 30.3	24.6 ± 11.7	0.012*
Major jerk/movements, mean ± SD	43.9 ± 29.1	15.8 ± 12.0	0.012*
Little jerks/minor movements, mean ± SD	231.9 ± 126.1	226.8 ± 157.8	0.889
Initiation of major motor events, mean ± SD	79.9 ± 40.8	14.9 ± 10.7	0.012
Violent motor events (initiation), mean ± SD	6.9 ± 5.2	0.1 ± 0.4	0.012**
Complex/scenic behavior (initiation), mean ± SD	29.0 ± 9.6	3.5 ± 2.8	0.012**
Major jerks/movements (initiation), mean ± SD	44.0 ± 30.9	11.3 ± 9.3	0.012**
Duartion (sec.), mean ± SD	8.9 ± 9.1	5.3 ± 4.7	0.004
Controls			
Mini epochs, mean ± SD	REM with REMs 476.1 ± 33.6	REM without REMs 1089.4 ± 440.2	*P*-value#
Violent motor events, mean ± SD	0	0	n.a.
Complex/scenic behavior, mean ± SD	0	0	n.a.
Major jerk/movements, mean ± SD	2.3 ± 2.7	2.8 ± 3.0	0.799
Little jerks/minor movements, mean ± SD	9.4 ± 8.0	13.4 ± 10.8	0.262
Initiation of major motor events, mean ± SD	2.1 ± 2.6	1.4 ± 1.5	0.750
Violent motor events (initiation), mean ± SD	0	0	n.a.
Complex/scenic behavior (initiation), mean ± SD	0	0	n.a.
Major jerks/movements (initiation), mean ± SD	2.1 ± 2.6	1.4 ± 1.5	0.750

* Following Bonferroni correction, *P*-values <0.0125 indicate statistical significance.
** Follwing Bonferroni correction, *P*-values <0.0167 indicate statistical significance.
# *P*-values were calculated using the Wilcoxon rank test for paired datasets. n.a., not applicable.

(threshold for significance 0.0125 for four variables). Moreover, a significant association between the initiation of major motor activity in the video and REM sleep with REMs was detected ($P < 0.0167$ for three variables following Bonferroni correction). In contrast, minor motor activity was evenly distributed between REM sleep with and without REMs ($P = 0.889$). Motor events in REM sleep with REMs were longer in duration than were those in REM sleep without REMs ($P = 0.004$).

In controls, the distribution of motor events of predominantly minor motor activity did not differ between REM sleep with and without REMs ($P > 0.05$). For detailed results see Table 4.

We further analyzed the association between motor events and the presence of phasic chin EMG activity (see Table 5). In patients with RBD and in controls, a trend of significance was revealed that did not withstand Bonferroni correction (see Table 5). No significant association was seen between chin EMG activity and the presence or absence of REMs (phasic EMG activity, $P = 0.484$; tonic EMG activity, $P = 0.208$).

Table 5
Relation between motor events and phasic EMG activity

Patients			
Mini epochs, mean ± SD	Phasic EMG 793.3 ± 258.3	No phasic EMG 1277.0 ± 1126.8	*P*-value[#]
Initiation of major motor events, mean ± SD	69.5 ± 23.6	25.3 ± 33.8	0.017
Violent motor events (initiation), mean ± SD	6.1 ± 5.5	0.9 ± 1.5	0.018[*]
Complex/scenic behavior (initiation), mean ± SD	26.1 ± 9.3	6.4 ± 9.5	0.025[*]
Major jerks/movements (initiation), mean ± SD	37.3 ± 18.4	18.0 ± 23.2	0.025[*]
Controls			
Mini epochs, mean ± SD	Phasic EMG 158.8 ± 74.0	No phasic EMG 1406.8 ± 487.5	*P*-value[#]
Initiation of major motor events, mean ± SD	2.3 ± 1.5	1.3 ± 1.2	0.071
Violent motor events (initiation), mean ± SD	0	0	n.a.
Complex/scenic behavior (initiation), mean ± SD	0	0	n.a.
Major jerks/movements (initiation), mean ± SD	2.3 ± 1.5	1.3 ± 1.2	0.071

[#] *P*-values were calculated using the Wilcoxon rank test for paired datasets.
[*] Following Bonferroni correction, *P*-values <0.0167 indicate statistical significance. n.a., not applicable.

4. Discussion

This is the first study to examine whether motor activity assessed by video recording and EMG in human RBD is more likely to be initiated in REM sleep with REMs than in REM sleep without REMs. Our aim in performing this work was to provide insights into the role played by these two different functional states of REM sleep in the pathogenesis of RBD.

The most important finding of the present study is a significant association between the initiation of major motor activity in RBD and REM sleep with REMs. Interestingly, a recent study has highlighted that the movements during RBD are elaborate, complex, non-stereotyped motor manifestations which might suggest they are generated by the motor cortex and bypass the basal ganglia [12]. Based on this hypothesis, our results might invite further speculation that these cortical movements not filtered by the basal ganglia are generated and transmitted specifically during REM sleep with REMs.

REM atonia or rather hypotonia, as found by a recent work analyzing muscle activity across sleep stages [17], is caused by an active glycinergic post-synaptic inhibition of the spinal alpha-motoneurons resulting in hyperpolarization and muscle atonia [18]. Even in physiological REM sleep, this muscle atonia is interrupted from time to time by twitches and jerks of the extremities, which we also observed in our study's control group. This paradoxical co-occurrence was resolved by investigations in animals showing that potent motor excitatory drives – reflecting descending excitatory activity emanating from supraspinal pathways – frequently occur during periods with REMs. In animals, ponto-geniculo-occipital (PGO) waves are closely related to muscle twitches, both of which are counted as phasic elements of REM sleep. PGO waves are generated in the pons by PGO burst cells. They are in close temporal association with ipsilateral eye movements in REM sleep [19]. The lack of complex behaviors during physiological REM sleep is explained by the preponderance of inhibitory influences of spinal motoneurons plus a reduced drive within locomotor generators [20]. In RBD, which is characterized by a loss of muscle atonia, it may be hypothesized that this phasic excitatory descending activity is disinhibited, and therefore major motor activity takes place instead of physiological twitches in the context of REMs. Alternatively, one might speculate that motor activity in RBD is not only associated with REMs, but that REMs are part of the disease itself, and that the underlying pathomechanism is not only characterized by a dyscontrol of the normal cortical motor output but also by an increased output of REMs and the related PGO waves. This hypothesis was not further supported by our data, which showed no difference in REM density between patients and controls. Nevertheless, a difference in the total number of REMs occurring in both groups cannot be excluded.

A changing spectrum of neuronal network activity has to be assumed for the transition between REM sleep with REMs and REM sleep without REMs. This interpretation is supported by a study in pontine-lesioned cats performed by Soh et al., who observed that most REM bursts were related to generalized body movements such as jumping or attacking [21].

Our results support the concept that an activation of different neuronal circuits underlies REM sleep with REMs and REM sleep without REMs. Functional characteristics of REM sleep with and without REMs have been investigated by positron emission tomography and functional magnetic resonance imaging studies [22]. In contrast to REM sleep without REMs, REM

sleep with REMs was associated with activation in the right lateral geniculate body, the posterior hypothalamus and the occipital cortex suggesting that REM sleep with and without REMs represent two distinct entities of stage REM [22]. Using a functional MRI paradigm, Wehrle and coworkers were recently able to demonstrate that REM sleep is not a uniform state, but consists of two distinct functional "microstates" that are characterized by functionally different neuronal circuits and different responsiveness to external stimuli [4].

Our data are congruent with the hypothesized mechanism of the therapeutic effect of clonazepam in RBD, [15,23] which is thought to decrease REMs and suppress phasic EMG activity by enhancing the inhibitory effect of serotonergic neurons located in the dorsal raphe nuclei on phasic features of REM sleep [15]. According to our findings, elaborate or violent motor activity is predominantly initiated during REM sleep with REMs.

In the controls, predominantly minor motor activity was present, with rare myoclonic body jerks. Concerning the temporal association with motor events on the video, minor motor activity was evenly distributed between REM sleep with REMs vs. REM sleep without REMs. This finding was in line with the patient group.

The association of major motor activity and phasic chin EMG activity slightly failed to achieve significance after Bonferroni correction. However, since most abnormal sleep behaviors seen in RBD involve movements of the limbs, one might speculate that by taking additional limb muscles into the analysis, the strength of this association could increase.

Unexpectedly, we found no association between chin EMG activity and the presence of REMs. One possible explanation might be that the physiologically descending excitatory potentials that override glycinergic muscle inhibition during REM sleep with REMs [18] are more visible in the limbs than in the chin.

RBD patients in this study comprise both CNS drug-naive patients and patients being treated with CNS active medication at time of polysomnography. Although no significant difference was seen between these two patient groups concerning REM sleep variables, REM sleep microstructure and motor events on the video, a potential influence of these medications can not be totally excluded because of the small sample sizes of the subgroups. In a non-RBD population, an increase in tonic EMG activity was observed in subjects taking selective serotonin reuptake inhibitors (SSRI), together with an increase in phasic EMG activity; although the latter did not reach statistical significance [24]. Moreover, a greater REM density in late-rebound REM periods was found for tricyclic antidepressants such as nortryptiline [25].

One potential drawback of our study is the possibility that minor motor events were underestimated, since most patients did not tolerate sleeping without a blanket. Therefore, especially minor movements of the lower extremities could have been missed. However, we do not think this substantially influenced our results concerning the association with REMs, since minor movements would also have been missed in REM sleep with and without REMs. We also safeguarded against a potential overrepresentation of small movements by counting only their presence or absence per mini-epoch, and not attempting to give an exact number of these movements. Furthermore, in order to minimize an observational bias, we proceeded strictly as lined out in Section 2 by (1) coding tonic and phasic EMG activity, (2) coding REM sleep with and without REMs and (3) analyzing motor events on the video in relation to REMs and phasic EMG activity.

In summary, this is the first study to show a close temporal association between major motor activity and REMs in RBD patients. Our data support the concept of a dual nature of REM sleep, namely with and without REMs. Since major motor activity is associated with and predominantly initiated in REM sleep with REMs, further studies should investigate REM sleep with REMs as a potential target in the treatment of RBD. Moreover, our findings imply a possible gate control mechanism of REM sleep with REMs in contrast to REM sleep without REMs for the manifestation of elaborate or violent behaviors in RBD.

Acknowledgements

We are grateful to Heinz Hackner for expert realization of video-polysomnograms, to Sybille Gasser, MD, for her dedicated and skillful patient care and PSG reading, and to Martin T. Furtner, MD, for critical reading of the manuscript.

This work was supported by Grant No. 9223, Anniversary Fund of the Austrian National Bank.

References

[1] Schenck CH, Hurwitz TD, Mahowald MW. Symposium: normal and abnormal REM sleep regulation: REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. J Sleep Res 1993;2:224–31.

[2] REM sleep behavior disorder. In: International classification of sleep disorders, 2nd ed. Diagnostic and coding manual. Westchester (IL): American Academy of Sleep Medicine; 2005. p. 148–52.

[3] Jouvet M, Delorme F. Locus coeruleus et sommeil paradoxal. C R Soc Biol 1965;159:895–9.

[4] Wehrle R, Kaufmann C, Wetter TC, et al. Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. Eur J Neurosci 2007;25:863–71.

[5] Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 1992;42:1371–4.

[6] Consens FB, Chervin RD, Koeppe RA, et al. Validation of a polysomnographic score for REM sleep behavior disorder. Sleep 2005;28:993–7.

[7] Eisensehr I, Linke R, Tatsch K, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. Sleep 2003;26:507–12.
[8] Bliwise DL, He L, Ansari FP, Rye DB. Quantification of electromyographic activity during sleep: a phasic electromyographic metric. J Clin Neurophysiol 2006;23:59–67.
[9] Sforza E, Zucconi M, Petronelli R, Lugaresi E, Cirignotta F. REM sleep behavioral disorders. Eur Neurol 1988;28:295–300.
[10] Fantini ML, Gagnon JF, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. Neurology 2003;61:1418–20.
[11] Iranzo A, Santamaria J, Rye DB, et al. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. Neurology 2005;65:247–52.
[12] De Cock VC, Vidailhet M, Leu S, et al. Restoration of normal motor control in Parkinson's disease during REM sleep. Brain 2007;130:450–6.
[13] Frauscher B, Gschliesser V, Brandauer E, et al. Video analysis of motor events in REM sleep behavior disorder. Mov Disord 2007;22:1464–70.
[14] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: Brain Information Service/Brain Research Institute; 1968.
[15] Mahowald MW, Schenck CH. REM sleep parasomnias. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: Elsevier Saunders Company; 2005.
[16] Gagnon JF, Bedard MA, Fantini ML, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 2002;59:585–9.
[17] Okura K, Kato T, Montplaisir JY, Sessle BJ, Lavigne GJ. Quantitative analysis of surface EMG activity of cranial and leg muscles across sleep stages in humans. Clin Neurophysiol 2006;117:269–78.
[18] Chase MH, Morales FR. Control of motoneurons during sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: Elsevier Saunders Company; 2005.
[19] Nelson JP, McCarley RW, Hobson JA. REM sleep burst neurons, PGO waves, and eye movement information. J Neurophysiol 1983;50:784–97.
[20] Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 2007;130:2770–88.
[21] Soh K, Morita Y, Sei H. Relationship between eye movements and oneiric behavior in cats. Physiol Behav 1992;52:553–8.
[22] Peigneux P, Laureys S, Fuchs S, et al. Generation of rapid eye movements during paradoxical sleep in humans. Neuroimage 2001;14:701–8.
[23] Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986;9:293–308.
[24] Winkelmann JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004;27:317–21.
[25] Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. Hum Psychopharmacol 2005;20:533–59.