Motor-Behavioral Episodes in REM Sleep Behavior Disorder and Phasic Events During REM Sleep

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Study Objectives: To investigate if sudden-onset motor-behavioral episodes in REM sleep behavior disorder (RBD) are associated with phasic events of REM sleep, and to explore the potential meaning of such an association.
Design: Observational review analysis.
Setting: Tertiary sleep center.
Patients: Twelve individuals (11 males; mean age 67.6 ± 7.4 years) affected by idiopathic RBD, displaying a total of 978 motor-behavioral episodes during nocturnal in-laboratory video-PSG.
Interventions: N/A
Measurements and Results: The motor activity displayed was primitive in 69.1% and purposeful/semi-purposeful in 30.9% of the motor-behavioral episodes recorded. Sleeptalking was significantly more associated with purposeful/semi-purposeful motor activity than crying and/or incomprehensible muttering (71.0% versus 21.4%, $P < 0.005$). In 58.2% of the motor-behavioral episodes, phasic EEG-EOG events (rapid eye movements [REMs], α bursts, or sawtooth waves [STWs]) occurred simultaneously. Each variable (REMs, STWs, α bursts) was associated more with purposeful/semi-purposeful than with primitive movements ($P < 0.05$).
Conclusions: Motor-behavioral episodes in RBD were significantly more likely to occur in association with phasic than with tonic periods of REM sleep. The presence of REMs, α bursts and STWs was found to be more frequent in more complex episodes. We hypothesize that motor-behavioral episodes in RBD are likely to occur when the brain, during REM sleep, is in a state of increased instability (presence of α bursts) and experiencing stronger stimulation of visual areas (REMs).
Keywords: REM sleep behavior disorder, rapid eye movements, α burst, sawtooth wave, phasic EEG events
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THE FUNCTIONAL CORRELATES OF PHASIC EVENTS OCCURRING DURING REM SLEEP ARE STILL NOT COMPLETELY UNDERSTOOD. RAPID EYE MOVEMENTS (REMs) are thought to be related to visual stimulation of occipital areas of the brain,[1] leading to activation of a neuronal loop involving mesial structures of the temporal lobe, which affect the emotional tone of dreams.[2] Visual[3] and spectral EEG analyses[4] have documented the presence of bursts of α activity (α bursts), unrelated to the occurrence of REMs, not associated with arousals and distinct from REM background α activity. It has been hypothesized that these may be "microarousals," reflecting a state of intra-REM vigilance fluctuation, which facilitates contact between the dreaming brain and the external world. REM phasic events have been associated with sudden-onset motor behavioral episodes and suggested to play some role in triggering or modulating them. Indeed, the literature contains reports of sudden, generalized body movements in a general picture of aggression in cats with REM without atonia,[5] palatal myoclonus in humans,[6] and focal motor and limbic epileptic seizures in experimental models of epilepsy.[7]
The aim of our study was to investigate whether the occurrence of motor-behavioral episodes in human REM sleep behavior disorder (RBD) is associated with PSG-defined phasic events of REM sleep and the potential meaning of such an association.

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PATIENTS AND METHODS

Patients

This study included 12 patients (11 males; mean age 67.6 ± 7.4 years, range 55-77, median age 70) affected by idiopathic RBD. All patients were diagnosed and followed up at the Sleep Medicine Unit of the "C. Mondino Institute of Neurology Foundation" over a 2-year period (2005-2007). The mean age of the patients at RBD onset was 61 ± 6.8 years, median 61.5 years (range 46-70); the disorder had been present for a mean of 7 ± 4.2 years, median duration 5.5 years (range 2-14). The patients had a mean Mini Mental State Examination (MMSE) score of 27.0 ± 1.5, range 25-30.

No patient had sleep disordered breathing or was taking any CNS-active drug.

METHODS

REM sleep behavior disorder was diagnosed on the basis of clinical data (face-to-face interview and semi-structured sleep questionnaire administered to the patient and his/her bed partner) and an overnight in-laboratory video polysomnography (video-PSG) recording performed according to standard criteria.[8] RBD secondary to other causes was ruled out by physical and neurological examinations, neuroradiological brain findings, and neuropsychological tests; the latter included the MMSE, in which a score of 24 was taken as the lower limit of normal in accordance with the normative value for the Italian population.[9]

Table 1—REM Sleep Data and Video-PSG-Recorded Clinical Manifestations (Motor Episodes With and Without Vocalizations; Episodes of Pure Vocalizations)

Subject	1	2	3	4	5	6	7	8	9	10	11	12
# of REM phases recorded	2	3	3	2	2	2	2	1	3	4	1	1
REM time (min)	51	79	64	46	18	36	19	7	29	86	13	40
Primitive motor episodes [with and without vocalizations]												
isolated	60	136	6	106	11	172	7	14	46	56	1	11
repetitive/rhythmic	1	0	0	0	1	1	0	0	0	22	0	0
Purposeful motor episodes [with and without vocalizations]												
facial expressions	14	10	21	8	6	1	0	0	0	45	7	37
gesturing, pointing	5	110	0	0	1	2	0	0	0	1	0	0
punching	6	2	0	0	0	4	0	3	1	0	0	0
kicking	0	0	0	3	0	0	0	0	2	1	0	0
Vocalizations only												
intelligible sleeptalking	2	14	0	1	0	0	1	0	1	1	2	1
incomprehensible muttering	0	5	0	1	0	0	0	0	0	0	1	1
crying	0	1	0	0	1	0	0	0	0	3	0	1

Procedures

All patients underwent a full-night in-laboratory video-PSG recording. Digital video PSG acquisition system used in this study displays video and PSG signals simultaneously on the same screen. This allowed us to perform a synchronised video-EEG analysis to look for integration of PSG activity with motor-behavioral activity. The PSG montages included: extended EEG montages (full-scalp EEG, positioning of leads according to the International 10-20 System: Fp1, Fp2, F3, F4, F7,F8,C3, C4, P3,P4,T3, T4, T5,T6,O1, O2, common reference, with display system used to allow the rearrangement of EEG traces into various montages); electrooculogram; electromyography of the chin, tibialis and deltoid muscles; recording of snoring by means of a microphone, of thoracic and abdominal respiratory movements by means of strain gauges, and of airflow by means of thermocouples located at the mouth and nostrils; EKG; body position; and measurement of oxyhemoglobin saturation ($HbSaO_2$) by means of a pulse oximeter with a finger probe.

The PSG recordings were scored, according to the AASM manual[10] for sleep staging (using the 30-sec epoch criterion) and for the evaluation of respiratory variables.

Analysis of Motor-Behavior Episodes

On the basis of video-audio-EMG analysis, the motor component of each RBD episode was categorized, according to the degree of complexity of the movements, as:

1) primitive: simple, jerky movements of the head, face, neck, trunk, arms or legs, hands or feet, or of the whole body, apparently without purpose, isolated or repetitive, arrhythmic or rhythmic; or

2) complex: semi-purposeful/purposeful movements, such as gesturing, pointing, punching, and kicking, appearing in isolation or in the context of a fighting-like sequence.

If more than one clearly detectable motor component was observed, or a progression from one type to another, the movement was categorized on the basis of the prevalent component. We also considered the presence of verbalization, in the form of shouting, crying, the emission of phonemes, and more or less articulate or intelligible sleep talking.

Analysis of PSG-Defined Events

Sawtooth waves (STWs) were defined as frontocentral, bilaterally synchronous, and symmetrical surface-positive, 2-5 Hz waves with an amplitude of 20-100 µV. To be included in the analysis, ≥ 3 consecutive waves had to be present.[11] Alpha bursts were well-defined bursts of α activity (7.5-12.5 Hz) with an amplitude ≥ 20 µV, occurring during REM sleep in the absence of increased EMG activity or spindles. To be counted as an α burst occurring during REM sleep, the REM period had to have started ≥ 1 minute before the occurrence of the α burst and had to continue ≥ 1 minute after it.[1] Rapid eye movements (REMs) were defined as rapid conjugate movements of the eyes, occurring in isolation or in bursts.

Analysis of the Relationship Between Motor-Behavioral Episodes and PSG-Defined Events

To define the relationship between RBD motor-behavioral episodes and PSG-defined events, the video-PSG recordings were scored in 5-sec epochs. When an episode lasted for ≥ 2 consecutive 5-sec epochs, only the first epoch was considered in the analysis. Motor-behavioral episodes were deemed to be related to PSG-defined events when both occurred in the same epoch. In other words, REMs, STWs, and/or α bursts had to be synchronous with the motor-behavior episodes; alternatively, if these phasic events started first, they were required to be present during the clinical manifestations or, at the very least, not to finish any sooner than 1 second after their onset.

All the analyses were conducted displaying the video-PSG recordings on the screen (as many times as necessary). Two doctors (M.T. and M.G.) scored them independently, categorizing the video-PSG patterns according to the established criteria. In the event of discordance between their scores, the 2 raters

Table 2—Figures of Association Between Motor-Behavioral Episodes and PSG-Defined Events

	Total	% of movements with REMs	% of movements with STWs	% of movements with α bursts	% of movements with two or more phasic events
Primitive movement	651	39.9	4.4	1.8	9.0
Purposeful/semi-purposeful movement	290	35.8	4.1	2.0	16.9
Vocalizations only	37	21.6	5.4	5.4	16.2

viewed the video-PSG together in order to reach a consensus. Discordance between observers was estimated to occur for approximately 4% of observations (44/978 observations).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Baltimore). Descriptive statistics are given as frequencies (percentages). For statistical purposes, each epoch was coded according to presence/absence of motor-behavioral episodes, REMs, SWTs, and α bursts. The presence/absence of movement was cross-tabulated in 2 × 2 tables with the presence/absence of REMs, SWTs, and α bursts. Fischer's exact test (χ^2) was used to test the association (cut off: P < 0.05).

RESULTS

Motor-Behavioral Episodes

A total of 978 (median 53.5; range 8-278) motor-behavioral episodes in 26 REM sleep periods were analyzed (Table 1). Of these episodes, 37 consisted of vocalizations only, and the other 941 movements or combinations of movements and vocalizations. In 651 of the 941 episodes with motor components (69.1%), the movement was classified as primitive, and in the remaining 290 (30.8%) it was classified as purposeful/semi-purposeful; in 25 of the 651 episodes with primitive motor activity, this activity was repetitive or rhythmic (3.8%).

The purposeful/semi-purposeful motor activity consisted of facial expressions (including laughing) in 149 (51.3%) episodes, gesturing or pointing in 119 (41.0%), punching movements in 16 (5.5%), and kicking movements in 6 (2.0%).

Overall, vocal manifestations were present in 82 episodes (37 purely vocal manifestations and 45 episodes of combined vocal and motor activity): the vocal manifestations consisted of intelligible sleep talking in 51 (62.2%) episodes, isolated phonemes or incomprehensible loud muttering in 21 episodes (25.6%), and crying in 10 (12.2%).

In the 45 (54.9%) episodes of combined vocal and motor activity, the vocal phenomena consisted of sleep talking in 31 episodes and crying and/or incomprehensible loud muttering in 14. These vocal phenomena were associated with purposeful/semi-purposeful movements in 71.0% and 21.4% of the episodes respectively (P < 0.005).

PSG-Defined Events and Motor-Behavioral Episodes

A total of 569 (58.2%) motor behavioral episodes were accompanied by at least one of the PSG defined events. The row, single figures of association between motor behavioural episodes and PSG defined events are shown in Table 2. Considering the motor behavioral episodes as a whole, 50.3% (P < 0.0005) of them were associated with REMs, 7.9% were associated with α bursts, and 11.7% were associated with STWs.

Univariate analysis showed that the occurrence of REMs (56.1% versus 48.1%, χ2 5.09, P=0.028), α burst (10.7% versus 6.1%, χ2 6.01, P=0.016) and SWTs (15.9% versus 10.0%, χ2 6.76, P=0.011) were more strongly associated with purposeful/semi-purposeful movements than with primitive movements. Vocalizations were associated with the presence of REMs (51.1%, P < 0.0005). It was not possible to rule out differences in the relationship with PSG-defined events in sleeptalking versus crying and/or incomprehensible loud muttering.

DISCUSSION

In accordance with data in the literature,[12,13] our RBD patients showed a wide variety of motor-behavioral manifestations. These ranged from simple, primitive movements to more complex movements (gestures, actions) occurring in isolation or in the context of what appeared to be, in most cases, the enactment of a fight with an aggressor. 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.

While the pattern of gross, jerky, sometimes apparently archaic movements of the whole body or of one of its parts seems to suggest that the movements arise from the activation of the central pattern generators in the brainstem-spinal cord,[14] the occurrence of more complex, elaborate movements (such as pointing, gesturing, punching) is more indicative of the possible involvement of motor cortical areas.[15,16] Even though, to date, no one has provided concrete evidence that focal cortical stimulations can give rise to RBD episodes, the electrical stimulation of cingulate gyrus is reported to trigger movements similar to those commonly seen in RBD episodes.[17]

It has recently been suggested, in a clinical and video-PSG investigation of RBD in Parkinson disease, that elaborate movements during RBD originate from the motor cortex, and that the inputs generated follow the pyramidal tract, bypassing the basal ganglia.[16] Given that the extrapyramidal system normally exerts an optimizing effect on movement execution,[18] its bypassing would explain why the movements, while complex, retain a jerky, rough quality. Different motor cortical areas may be activated, resulting in patterns of varying complexity.

It is known that in REM sleep there is strong visual stimulation of the occipital and posterior areas of the brain[1]; it is as though the dreaming subject , experiencing hallucinatory dream imagery, were watching a scene unfold before him (usually a frightening one in RBD); as a result, the patient is in a condition very similar to that in which, during wakefulness, there occurs an activation of the complex visuo-motor loop that includes the mirror neurons.[19] The mirror neuron network, first discovered in the monkey (*Macaca nemestrina*), has been shown to exist in the human brain as well. It involves a frontoparietal and insular-cingulated circuitry in which the same neurons have been found to be activated both by the execution and by the mere observation of actions.[20] In short, the neuronal mirror system, in which observation of an action activates cortical networks that are the basis of the execution of that same action, emerges as potentially capable of generating highly integrated sensory-motor behaviors.[21] The activation of this loop during RBD might account for the more complex motor-behavioral episodes in this disorder (movements, gestures following a clear pattern in the context of a definite action).

We found that motor-behavioral episodes in RBD were significantly more likely to occur in association with phasic than with tonic periods of REM sleep. Yet the presence of α bursts and REMs was found to be more frequent in more complex episodes characterized by elaborate movements in association with quite fluent, often even intelligible sleep talking.

Rapid eye movements are thought to be related to visual stimulation of occipital areas of the brain[1] and microarousal-like periods have been hypothesized to occur in temporal association with α bursts.[3] Taken together, these data suggest that motor-behavioral episodes in RBD are likely to occur when the brain, during REM sleep, is in a state of increased instability (presence of α bursts) and experiencing stronger stimulation of visual areas (REMs), and they indicate a further potential functional significance of these phasic PSG-defined events.

Our study presents several methodological limitations. The cohort was small, and some of the patients contributed disproportionately to the overall number of episodes analyzed. The results were also weakened by the impossibility of establishing whether or not there is intersubject variability and, if there is, whether it is real (i.e., independent of the number of events sampled) or, instead, a function of varying cases contributing different numbers of events.

Our study was a standard clinical-PSG observational investigation and did not make provision for further exploration (neurophysiological or functional imaging) of brain functional state/reactivity.

The patients sometimes slept under sheets or blankets, which may have reduced the accuracy of the video observations. Finally, PSG montages did not include monitoring of other muscle groups (such as distal arms flexors) that are known to display most activity in phasic REM sleep and might have provided further insight into the unit of analysis considered in the study (behavior plus or minus PSG-defined phasic events).

Despite these limitations, this study is, to the best of our knowledge, the first to focus on the potential relationship between motor-behavioral episodes in idiopathic RBD and PSG-documented, particularly EEG events, during REM sleep. Further studies, possibly integrating EEG and brain imaging data, are needed to support our preliminary findings. Such studies could help to improve understanding of the physiopathogenesis of RBD.

POST SCRIPT

After the acceptance of our work, we became aware of the paper, *The relation between abnormal behaviors and REM sleep microstructure in patients with REM sleep behavior disorder*. Frauscher B, Gschliesser V, Brandauer E, Ulmer H, Poewe W, Högl B. Sleep Med. 2008 Mar 21. [Epub ahead of print], focusing on the relationships between REMs and motor events in RBD. It was too late to discuss our data, concerning both REMs and EEG REM phasic events with respect to motor behavioral manifestations in RBD, in light of the ones in this work and to cite it in the References. However we are pleased to acknowledge the paper now, stressing the concordance between Frauscher et al. and our data in indicating a facilitating effect of phasic periods of REM sleep on the occurrence of complex motor behavioral episodes in RBD.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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