Electroencephalographic alpha band power enhancement during rapid eye movement sleep in rapid eye movement sleep behavior disorder

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Abstract
Objective Rapid eye movement (REM) sleep behavior disorder (RBD) is a common sleep disorder in the elderly. We aim to reveal the physiological mechanism underlying RBD by analyzing changes in the electroencephalographic (EEG) spectrum during REM sleep.

Methods Twenty patients with RBD monitored using video polysomnography and 13 age-matched healthy volunteers were enrolled. The EEG signal was acquired using an average reference electrode. A Fourier transform was performed on both EEG data. Furthermore, the absolute power values and relative power values of five different frequency bands were calculated. The range of each frequency band was defined as follow: δ: 0.5–3 Hz, θ: 4–7 Hz, α: 8–13 Hz, β: 14–30 Hz, and γ: 30–35 Hz. The normal distribution of EEG power was tested compared using the t-test.

Results The dominant frequency band with the most power on EEG was θ band in both groups. Compared with control group, the RBD group had obvious power enhancement in α band. However, δ/α and θ/α power ratios in the RBD group were significantly lower than those in the control group.

Conclusion The cerebral cortex is hyperactive in RBD. This phenomenon may associate with higher power in the alpha band, which is similar to that observed when the skeletal muscle is not atonic. The cerebral cortex is involved in RBD neuropathic disorders as well as skeletal muscle achalasia. Our finding could provide a new method for improving RBD treatment via the moderate inhibition of cerebral cortex hyperactivity.

Introduction
Rapid eye movement sleep behavior disorder (RBD) is a sleep disorder characterized by abnormal behavior during rapid eye movement (REM) sleep. The behavior is related to dreaming and is mostly violent. Patients with RBD frequently cause self-injury or injure their bed partner. The proportion of injuries in sleep can reach as high as 32–65% [1] and potential injuries include falling from bed, bruises, fractures, and lacerations, among others[2]. RBD is a relatively common sleep disorder with a population prevalence of 0.4% to 0.5%[3] and the incidence in the elderly population can reach 2–6% [4, 5]. Male patients are more common, accounting for 80–90% of patients[6].

RBD can be divided into idiopathic RBD (iRBD) and secondary RBD. iRBD is closely related to α-
synuclein diseases, such as Parkinson’s disease, dementia with Lewy body, and multi-system atrophy, and often precedes the onset of such diseases, with a conversion rate of about 50% in 5 years and a conversion rate of 80% after 15 years[7]. Secondary RBD can be caused by brain stem injury associated with REM phase muscle loss, such as that secondary to vascular, inflammatory, or neoplastic disease, as well as certain diseases that affect brainstem function, such as narcolepsy and multiple sclerosis[8]. Drug-induced factors can also lead to secondary RBD, such as taking antipsychotics, serotonin reuptake inhibitors, or benzodiazepines, among others[2, 9].

RBD is related to the events of the patient’s dreams and its movements are usually highly coordinated, similar to conscious movements during wakefulness, suggesting that the motor cortex may participate in RBD movements; in addition, cone beam neurons that mediate limb autonomic movement are active during wakefulness and REM sleep[10], also suggesting the involvement of the motor cortex. Therefore, the functional status of the cerebral cortex and its influence on neural pathways during the onset of RBD may be a primary target for RBD research. Electroencephalography (EEG) can reflect the function of the cerebral cortex and state of consciousness through the bioelectrical activity of the cerebral cortex. A number of studies have reported the use of EEG in RBD studies. Jun Sang et al. calculated the weighted phase lag index as a measure of the functional connection of the awake resting EEG brain network and analyzed the small changes in the brain network in the early stages of RBD[11]. Raffaele Ferrari calculated the power of different frequency bands of the EEG in each sleep period of RBD and analyzed the stability of the EEG[12]. The above research mainly focused on the RBD awake brain network and power spectrum analysis of different frequency bands during sleep and does not reflect the functional status of the brain during RBD-related abnormal behavior. This study intends to reveal the corresponding functional state of the cerebral cortex by studying changes in the EEG power spectrum during REM sleep, especially during abnormal behavior, and reveal the possible mechanisms of RBD from a neurophysiological and informatic perspective.

Materials And Methods
 Twenty patients with iRBD from the Department of Neurology, Tianjin Medical University General Hospital from 2015 to 2017 were selected as the RBD group, with an average age of 62.3±9.2 years and male to female ratio of 15:5. Thirteen volunteers, age- and sex-matched with the RBD group, were recruited as a healthy control group (HC group) with an average age of 59.8 ± 11.0 years and male to female ratio of 10:3. All RBD patients were diagnosed in accordance with the third edition of the International Classification of Sleep Disorders and the following three types of conditions were excluded: 1) diseases affecting brain blood vessels, causing inflammation, neoplastic disease, degenerative disease, and other neurological diseases that cause changes on brain imaging; 2) diseases including epilepsy, Alzheimer’s disease, and other silent diseases, such as neurological diseases that cause changes on EEG changes; and 3) diseases including Parkinson's disease, multiple system atrophy, Lewy body dementia, narcolepsy, and other neurological diseases with RBD. The HC group were specifically screened to exclude participants with sleep disorders, neurological diseases, or mental illnesses. No antipsychotics, antidepressants, anxiolytic, sedative hypnotics, monoamine oxidase inhibitors, alcohol, or coffee were consumed by members of either group. This study was approved by the medical ethics review board.

Both groups underwent standard nighttime video polysomnography (v-PSG), including EEG, myoelectric recording (bilateral infraorbital and tibialis anterior muscles), thermal airflow, chest and abdomen breathing exercises, ocular electricity, and electrocardiogram. Sleep breathing parameters, such as snoring, pulse, oxygen saturation, and body position were also recorded. Both groups arrived at the monitoring room at 4 pm to adapt to the unfamiliar environment and reached a target sleep duration of 7 hours. The two groups had an apnea hypopnea index (AHI) <5. Two experienced professional medical workers jointly interpreted the pictures, staged sleep according to the standard of 30 seconds per frame, and interpreted dream-related behaviors such as increased muscle tension during REM sleep and nightmare-related limb movement. The EEG signal was collected using a Nicolet-V32 video electroencephalograph. The electrodes were placed in accordance with the international 10/20 system. The recorded frequency range was 0.5–35 Hz, the sampling rate was 256 Hz, the sampling accuracy was 16 bits, and the EEG leads were used in the average reference mode.
In both groups, EEG data from the REM phase with fewest artifacts was selected. RBD may be associated with increased mandibular electromyographic signal or dream-related behaviors. The signal was acquired using the average reference lead mode. After any leads with an artifact were excluded, the two groups were analyzed based on either the O1/Av or O2/Av lead.

Five segments of data with few baseline smooth artifacts were selected for analysis and each segment was 10 seconds long. Using the Matlab platform, after removing artifacts such as correcting for baseline signal, ocular-related signal, myoelectricity, ECG, and power frequency, the power of five different frequency bands was calculated following Fourier transformation (the range of each frequency band was defined as δ: 0.5–3 Hz, θ: 4–7 Hz, α: 8–13 Hz, β: 14–30 Hz, and γ: 30–35 Hz) and the average absolute power value and relative power ratio of the five segments of data were calculated. Normal distribution tests were performed on the two groups of average power values and significant differences were compared using a t-test (p<0.05).

Results

1. Comparison of sleep-related parameters between NC group and RBD group

Table 1. Sleep-related parameters of NC group and RBD group

| Variable                  | HC group (n=13) | RBD group (n=20) | P value |
|---------------------------|-----------------|------------------|---------|
| Age (year)                | 59.8±11.0       | 62.3±9.2         | 0.3     |
| Total recording time (minutes) | 515.5±67.8      | 561.4±63.3       | 0.04*   |
| Total sleep duration (minutes) | 395.7±69.8      | 370.45±94.3      | 0.2     |
| Sleep latency (minutes)   | 22.4±24.6       | 19.5±22.6        | 0.4     |
| REM latency (minutes)     | 108.8±53.5      | 177.8±148.4      | 0.04*   |
| Percentage of NREM-I (%)  | 9.1±5.5         | 15.8±9.6         | 0.01*   |
| Percentage of NREM-II (%) | 61.2±11.2       | 58.8±12.4        | 0.3     |
| Percentage of NREM-III (%)| 11.8±7.2        | 8.7±8.2          | 0.1     |
| Percentage of REM sleep (%)| 17.8±7.5        | 16.8±5.9         | 0.3     |
| Sleep efficiency (%)      | 76.6±10.9       | 65.9±18.9        | 0.03*   |
| PLMS index                | 6.8±11.5        | 9.4±12.1         | 0.3     |

(*P<0.05)

In this study, 13 HC volunteers and 20 iRBD patients were evaluated. The age and polysomnography parameters of the two groups are shown in Table 1. The total recording duration refers to the time from turning off the lights to turning on the lights; the total sleep duration refers to the sum of the duration of phase I, II, III, and REM sleep; the sleep latency refers to the time between when the light was turned off to the first frame of sleep; REM latency was defined as the time between the first frame of sleep to the first frame of the REM period; sleep efficiency (%) refers to the total sleep
duration\times100/total\ recording\ duration. The results show that there were significant differences between the two groups regarding total recording duration (P=0.04), REM latency (P = 0.04), stage I sleep as a percentage of total sleep (P = 0.01), and sleep efficiency (P = 0.03). Compared with the HC group, the sleep latency of the REM group was greater, sleep structure was more abnormal, and sleep efficiency was lower. In general, the sleep quality of the RBD group was worse than that of the HC group.

2. Comparison of EEG power spectrum in REM the phase between the HC group and RBD group

2.1 Comparison of absolute power values in each frequency band

Table 2. Comparison of power between HC group and RBD group

| Band | HC group power (μV2/Hz) | RBD group power (μV2/Hz) | Two groups of difference percentage (%) |
|------|------------------------|--------------------------|----------------------------------------|
| δ    | 0.2187                 | 0.2212                   | +1.14%                                 |
| θ    | 0.398                  | 0.4199                   | +5.50%                                 |
| α    | 0.1946                 | 0.2545                   | +30.78%                                |
| β    | 0.105                  | 0.1376                   | +31.05%                                |
| γ    | 0.0103                 | 0.01304                  | +26.60%                                |

Figure 1. Comparison of absolute power values of each frequency band in the HC group and RBD group

As can be seen in Table 2 and Figure 1, compared with the HC group, the α power of the REM phase of the RBD group was significantly enhanced (p < 0.05), while there was no significant difference between the two groups in the δ, θ, β, and γ power. The dominant frequency band with respect to power in the REM phase EEG in the HC group and RBD group was the θ band in both groups.

2.2 Comparison of relative power ratios of each frequency band

Figure 2. Ratio of each frequency band to α power

Figure 2. a, b, c, and d show the δ, θ, β, and γ to α power ratios of the HC group and RBD group, respectively. Compared with those of the HC group, δ/α, θ/α, and γ/α power ratios in the RBD group were lower and the β/α power ratio was higher. The difference in δ/α and θ/α power ratios was statistically significant (p < 0.05)

Discussion

Iranzo et al. found that the δ and θ powers of the RBD group were increased and the α and β powers were reduced compared with the HC group[7]. Maria Livia et al. studied patients with RBD during
wakefulness and found that the $\theta$ power in the frontal, temporal, and occipital regions was significantly enhanced and the $\beta$-power in the occipital region was significantly reduced. In the REM sleep phase, only the $\beta$-power of the occipital region was decreased, suggesting that cortical activation of the occipital region was impaired[8]. Raffaele et al. confirmed EEG instability during REM sleep in RBD patients, while the mean EEG power was not significantly affected [2]. The results of this study show that compared with the HC group, the $\alpha$ power in the RBD group during REM sleep was significantly enhanced, inconsistent with the above results. This may be because this study focuses on the analysis data obtained during the REM phase, especially during abnormal behavior and selects more dream-related behaviors. The EEG signal from the average reference lead, used to obtain a more stable EEG signal, shows a significant difference in alpha power. It indicates that the cerebral cortical function of RBD patients has changed in REM sleep, especially during the period of dreaming. Figure 2 shows that the slow-wave frequency band ($\delta$, $\theta$) to $\alpha$ power ratio are significantly specific and there may be no significant change in the $\delta$ and $\theta$ band powers of the RBD group, while the $\alpha$-band is significantly enhanced, indicating cerebral cortical function during RBD. The change is only related to the $\alpha$ band, but not to other neural bands, including the characteristic $\theta$ band.

John Peever et al. pointed out that REM sleep neuropathic disorders are the basis of RBD disease physiology[9]. They state that in patients with RBD the dorsal nucleus-ventral giant cell reticular nucleus (SLD-GiV) pathway in the dorsal ganglion cannot inhibit spinal motor neurons, allowing them to accept the excitatory projection of the motor cortex, thereby producing motor behavior during REM sleep. McKenna et al. also suggested that during the REM phase, the lower dorsal side of the RBM sleep neuron was degenerated by the nucleus-ventral medial medulla (Sub-VMM), preventing it from inhibiting motor neurons, leading to REM sleep achalasia, resulting in excessive muscle activity and exercise-like behavior [10].

V-PSG monitoring can be used to observe the achalasia of the mandibular or tibialis anterior muscles of RBD patients. The cerebral cortical function changes in RBD may be similar to skeletal muscle achalasia, both of which are involved in RBD neuropathic disorders. Increased alpha power suggests the hyperactivity of the cerebral cortex, which is similar to what is seen during skeletal muscle
activity. The α-rhythm is the main brain wave of EEG in the resting state during wakefulness. The increased α power indicates that the RBD group cannot enter the inhibited state like the HC group. Although the frequency band with dominant EEG power during the REM phase is still the θ band, the increase in α power may suggest that the cerebral cortex is over-inhibited and hyperactive.

Figure 3 shows that in the REM phase, descending SLD neurons activate gamma-aminobutyric acid (GABA) and glycinergic neurons in the GiV nucleus, continue to descend, and project to spinal skeletal motor neurons, resulting in REM muscle relaxation. Another group of ascending SLD neurons activates the thalamic cortical neurons, which in turn activate the cortex. In normal REM sleep, the SLD-GiV pathway inhibits spinal motor neurons and motor neurons block projections from the motor cortex. In RBD patients, the SLD-GiV pathway has degenerated, resulting in the loss of inhibition of motor neurons, which in turn allows motor neurons to project from the motor cortex [9].

Of course, the physiological mechanism of RBD is also related to the locus coeruleus, dorsal sulcus, substantia nigra, and lateral hypothalamus [11-13]. Neuronal degeneration leads to neurotransmitter disorders, such as GABA- and glycine-mediated loss of motor neuron inhibition [14-17].

This study found that during RBD, the cerebral cortex may be more active than during healthy REM sleep. Therefore, the degeneration of the SLD-GiV pathway causes it to attenuate spinal motor neurons activation in the descending pathway, and it is speculated that there may be another upstream pathway, which is also mediated by neurotransmitters, that also weakens the inhibition of this upward pathway. The cerebral cortex excitability is increased. The amygdala is the main nucleus that deals with negative emotions such as anger [18, 19]. In view of the fact that most dreams have violent content, it may weaken the inhibition of related nuclei in the amygdala. These nuclei are related to violent emotions, leading to excessive cerebral cortical activity and increased violent dreams.

Excessive cerebral cortical activity is another important phenomenon of RBD, in addition to muscle achalasia. Moderately inhibiting the cerebral cortex may be of great significance in the treatment of RBD. Li SX and other studies have shown that taking moderate doses of clonazepam can improve the dreams of RBD patients and reduce their dream-related behaviors such as speech and physical
activity, but the patient’s persistent and temporal myoelectric activity increases [20]. Therefore, clonazepam can effectively treat patients with RBD, an effect that may be closely related to the inhibition of cerebral cortex hyperactivity.

Declarations

**Compliance with Ethical Standards**

The study conforms "International ethical guidelines for biomedical research involving human subjects (2002) " developed by Council For International Organizations Of Medical Sciences (CIOMS) in collaboration with World Health Organization (WHO), researchs in this article are approved by Ethical Committee of Tianjin Medical University General Hospital. Informed consents are signed by all the patients. The Ethical Number is IRB2019-WZ-169.

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**Conflict of Interest**

The authors declare no conflict of interest.

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Figures
Figure 1

Comparison of absolute power values of each frequency band in the HC group and RBD group
Figure 2

Ratio of each frequency band to $\alpha$ power
Figure 3

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