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Age-related effects of bilateral frontal eye fields lesions on rapid eye movements during REM sleep in rhesus monkeys

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Abstract

Rapid eye movement (REM) is one of the most characteristic features of REM sleep, but the mechanisms underlying its regulation remain unclear. The present study aims to investigate whether the frontal eye field (FEF) is involved in the regulation of the rapid eye movements during REM sleep. To address this question, we ablated the FEF in four rhesus monkeys and observed the effects of the lesions on sleep architecture. After lesions, two adult monkeys did not show any lesion effect. However, in the other two adolescent monkeys, both the total duration and percentage of the rapid eye movements during REM sleep were decreased moderately. The result suggests that the relation between the FEF and the regulation of the rapid eye movements during REM sleep may be affected by age factor, also indicating that both the functions of the FEF and the mechanisms underlying the control of rapid eye movements during REM sleep might not be the same throughout the whole life span of an animal.

Keywords: Eye movement; Rapid eye movement sleep; Frontal eye field; Cortex lesion; Adolescence; Rhesus monkey

In 1953, for the first time, Aserinski and Kleitman reported "rapid, jerky and binocularly symmetrical" eye movements during a stage of sleep [2]. Their paper started the contemporary history of REM sleep research. There is now an extensive literature on both the biological functions [12,13,31] and the neural underpinnings [14,27] of REM sleep. However, our knowledge about the rapid eye movements, one of the most characteristic features of REM sleep, is still limited.

Previous researches indicated that the rapid eye movements during REM sleep and eye movements executed during wakefulness have different characteristics, including the spatio-temporal pattern [6,17,18], the binocular coordination [35] and brain potentials associated with the saccades [26]. Nevertheless, although the neural mechanisms underlying the control of eye movements during wakefulness have been investigated extensively [30,32], their counterparts controlling eye movements during REM sleep still remain unknown.

In the present study, we aim to investigate whether the frontal eye field (FEF) is involved in the regulation of eye movements during REM sleep in monkeys. The FEF, located in the prefrontal cortex, is a very important area for oculomotor control in primates (see Ref. [33] for review). Saccadic eye movements can be elicited with the electrical stimulation over the FEF. Many cells within the FEF discharge when the subject performs eye movement tasks, including saccade, fixation and smooth pursuit eye movements. Moreover, lesions or inactivation of the FEF severely impairs some aspects of eye-movement control. Although the roles of the FEF in oculomotor control during wakefulness are well documented, whether the similar roles exist during REM sleep is unknown. To address this question, we ablated the FEF bilaterally in four rhesus monkeys and studied the effects of the lesions on the rapid eye movements during REM

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sleep. Further, in order to investigate the developmental course of this subject, the experimental animals have been divided into two age groups, adolescent and adult.

Subjects for this study were two adult (11–12 years old, abbreviated as M1 and M2 in the rest part of the paper) and two adolescent (about 3 years old, M3 and M4) female rhesus monkeys (*Macaca mulatta*). Previous studies showed that wakeful activities could influence and alter subsequent sleep [10,15,22]. To obviate such possible interferences, the monkeys were housed in separate cages in animal rooms under standard conditions, without any behavioral tasks during the whole experimental period. This study was performed in accordance with the Guide for the Care and Use of Laboratory Animals adopted and promulgated by the National Institutes of Health.

Firstly, the Electroencephalogram (EEG) and the Electrooculogram (EOG) electrodes were implanted. The surgery was performed under anesthesia induced by hydrochloric acidulated ketamine (10 mg/kg, i.m.) and maintained by sodium pentobarbital (30 mg/kg, i.m.). The monkey's scalp was incised and retracted along with the muscles overlying the skull. Then the skull was cleaned and the Teflon-insulated epidural stainless steel recording electrodes (0.2 mm in diameter) were placed at the supraorbital areas and skull overlying the occipital cortex to record EOG and EEG signals, respectively. They were referenced to a midline electrode midway between the occipital ridge and the nasion. All electrodes were fixed on the skull by applying the dental cement. All surgical procedures were performed with the use of sterile techniques.

After two weeks of recovery following the electrodes implantation, the sleep adaptation and recording sessions began. Sleep was recorded while the monkeys were in a primate-restraining chair with their heads free. This setup enabled us to record the electrophysiological and video signals (see below) reliably. Earlier studies in several primate species suggested that the sleep architecture is not significantly disturbed when animals are chair-adapted [4,5]. To habituate the animals to the recording conditions, they were placed in the chair during the night daily for at least one week prior to the sleep recording. During the recording session after adaptation, the monkeys were placed in the restraining chair at approximately 17:00 h and lights were turned off at 18:00 h. Recording began at 22:00 h. EEG and EOG signals were on-line digitalized (500 Hz) and displayed on a screen. The behavior of the monkeys, including head movements, twitches of face and rapid movements of the external ears, were monitored continuously with an infrared video camera. A second mini-infrared camera, which was attached to the monkey's head and placed in front of the left eye of the animal, was used to monitor the eye movements clearly. The two video signals, along with the waveforms of EEG and EOG, were videotaped simultaneously through a video processor. Recording ended at 06:00 h in the next morning and the lights were turned on at 06:30 h. Then the animals were returned to their home cages. Each monkey's sleep was recorded for 10 days before FEF lesions.

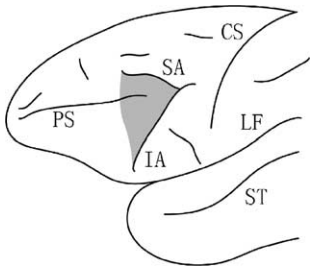

Fig. 1. Schematic diagram of the left hemisphere FEF lesion. It is representative of the lesion in the opposite hemisphere. The lesion is denoted by the shaded area on the lateral view. PS, principal sulcus; SA, superior limb of the arcuate sulcus; IA, inferior limb of the arcuate sulcus; CS, central sulcus; LF, lateral fissure; ST, superior temporal sulcus.

For bilateral FEF lesions, general anesthesia was established by using the methods described above. The lesions were made by aspiration under aseptic conditions. A trephine opening in the skull above the FEF was made to expose the whole arcuate sulcus, providing a clear view for lesion operations. The region lying within the rostral bank of the posterior curve of the arcuate, extending anteriorly over the lip of the arcuate, was aspirated under visual inspection with a suction cannula (Fig. 1). According to previous studies, these lesions covered the regions involved in both saccades and smooth pursuit eye movements [8,11,19]. At the end of recording session after the lesions, the first monkey (M1) was sacrificed by receiving a lethal dose of sodium pentobarbital. The brain was removed and the FEF lesions were confirmed histologically. After the lesion procedure was proved effective in the first monkey, the same lesions were made in the rest of the animals. At the end of the experiment, the FEF lesions in M4 were also confirmed histologically and no difference was detected between the lesions in adult (M1) and adolescent (M4) animals.

In order to minimize the posttraumatic sleep disturbance caused by the surgical operation of lesions, sleep recordings were preformed three weeks after the lesion surgeries, following two weeks of recovery and one week of adaptation, and lasted for 14 days.

Sleep records were staged according to the primate sleep staging criteria of EEG, EOG and behavior, and the durations of rapid eye movements were obtained by observing the video signals derived from the camera placed in front of the monkey's left eye. The isolated eye movements and bursts were not differentiated in the analysis. The videotape was played in normal or slow speed to show the onset and end of each eye-movement episode. Intervals longer than 5-s without any rapid eye movement were used to partition two consecutive episodes. We only analyzed the rapid eye movements during REM sleep. The fast or 'saccadic-type' movements have specific characteristics and a clear-cut border with eye movements that occur during other sleep stages [6]. Thus the total time of those movements can be recorded

accurately. In addition, the rapid eye movements sometimes begin before a REM episode (judged by EEG and behavior such as head resting on the shelf caused by the muscular atonia). It makes the duration of rapid eye movements sometimes longer than that of REM sleep in our observation (see results below) and in some other studies as well (e.g., Ref. [3]).

Data are presented as means ± S.D.s. Sleep parameters before and after the FEF lesions were compared by *t*-test in individual experimental animals. Each sleep parameter was assessed separately, with *P* value less than 0.05 as indicator of statistical significance.

Sleep parameters for the individual experimental animals are shown in Table 1.

The adult monkeys did not show any significant effect of the FEF lesions. As shown in Table 1, the sleep efficiency, both the total time and the percentage of slow wave sleep (SWS), REM sleep, rapid eye movements during REM sleep and the rapid eye movements to REM sleep ratio were not changed after the FEF lesions in the two adult monkeys. Contrastingly, in adolescent monkeys, while the sleep efficiency and SWS were unchanged after the lesions, the duration of both REM sleep and rapid eye movements during REM sleep were decreased moderately. The total time of REM sleep was decreased 8% for M3 and 10% for M4, and the percentage of REM sleep was decreased 10% (M3) and 8% (M4), respectively. Simultaneously, the total time of rapid eye movements during REM sleep was decreased 13% for M3 and 22% for M4, and its percentage was decreased 15% (M3) and 21% (M4), respectively. In addition, the ratio of rapid eye movements to REM sleep was also decreased in the two adolescent animals, suggesting that the amount of rapid eye movements was decreased more than that of REM sleep.

Moreover, the change patterns of sleep parameters in M1 and M2 did not show any consistency ($r = -0.60$, $P = 0.12$, see Fig. 2A), suggesting that the sleep parameters were not affected by the FEF lesions systematically in the two adult monkeys. However, the change pattern in M3 was correlated well with that in M4 ($r = 0.80$, $P = 0.02$, see Fig. 2B), further indicating that the FEF lesions affected the sleep architecture in the same manner in the two adolescent animals.

Our result shows that the FEF lesions did not affect the amount of rapid eye movements during REM sleep in adult monkeys. However, the lesion effect in adolescent monkeys is different significantly.

Table 1
Sleep parameters for the individual experimental animals

Sleep parameters	M1					M2				
	Normal ($n = 10$)		Lesion ($n = 14$)		*t*-test, two-tailed *P*	Normal ($n = 10$)		Lesion ($n = 14$)		*t*-test, two-tailed *P*
	Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.	
Adult monkeys										
Sleep efficiency (%)	78.6	8.7	82.7	4.5	0.199	94.3	2.9	95.3	3.9	0.473
SWS duration (min)	51.1	11.0	48.8	7.5	0.573	64.1	14.2	66.9	8.9	0.586
SWS percentage (%)	13.5	2.2	12.3	2.0	0.204	14.2	3.4	14.6	1.9	0.732
REM sleep duration (min)	53.9	4.6	51.9	7.5	0.413	79.8	9.6	83.8	9.5	0.320
REM sleep percentage (%)	16.5	1.8	14.9	2.0	0.062	17.6	1.9	18.3	2.1	0.393
Eye movements duration (min)	53.4	5.0	52.5	6.8	0.708	89.9	7.2	90.3	10.6	0.910
Eye movements percentage (%)	16.3	2.2	15.1	1.8	0.166	19.9	1.4	20.2	2.6	0.722
Rapid eye movements to REM sleep ratio	99.1	6.7	101.7	8.7	0.412	113.5	10.5	108.2	12.3	0.274
	M3					M4				
	Normal ($n = 10$)		Lesion ($n = 14$)		*t*-test, two-tailed *P*	Normal ($n = 10$)		Lesion ($n = 14$)		*t*-test, two-tailed *P*
	Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.	
Adolescent monkeys										
Sleep efficiency (%)	94.1	2.5	96.4	3.1	0.052	98.8	2.0	97.4	2.3	0.137
SWS duration (min)	84.4	15.6	76.8	12.5	0.218	78.8	15.8	69.1	10.6	0.111
SWS percentage (%)	18.7	3.2	16.6	2.8	0.124	16.6	3.3	14.8	2.2	0.145
REM sleep duration (min)	99.4	9.7	91.6	7.2	0.046*	75.1	4.7	67.8	8.7	0.015*
REM sleep percentage (%)	22.0	2.3	19.8	1.5	0.017*	15.8	0.9	14.5	1.7	0.019*
Eye movements duration (min)	107.8	9.6	94.2	7.2	0.002**	88.5	5.0	68.9	9.5	<0.001 **
Eye movements percentage (%)	23.9	2.3	20.4	1.5	0.001**	18.7	1.1	14.7	1.9	<0.001 **
Rapid eye movements to REM sleep ratio	108.6	5.6	102.9	2.2	0.011*	118.3	11.2	101.9	8.7	0.001**

The sleep efficiency is calculated as the ratio of the total sleep time to total recording time. SWS, slow wave sleep; The SWS (REM sleep/eye movements) percentage is the ratio of total duration of SWS (REM sleep/rapid eye movements) to total sleep time.

* $P < 0.05$.

** $P < 0.01$.

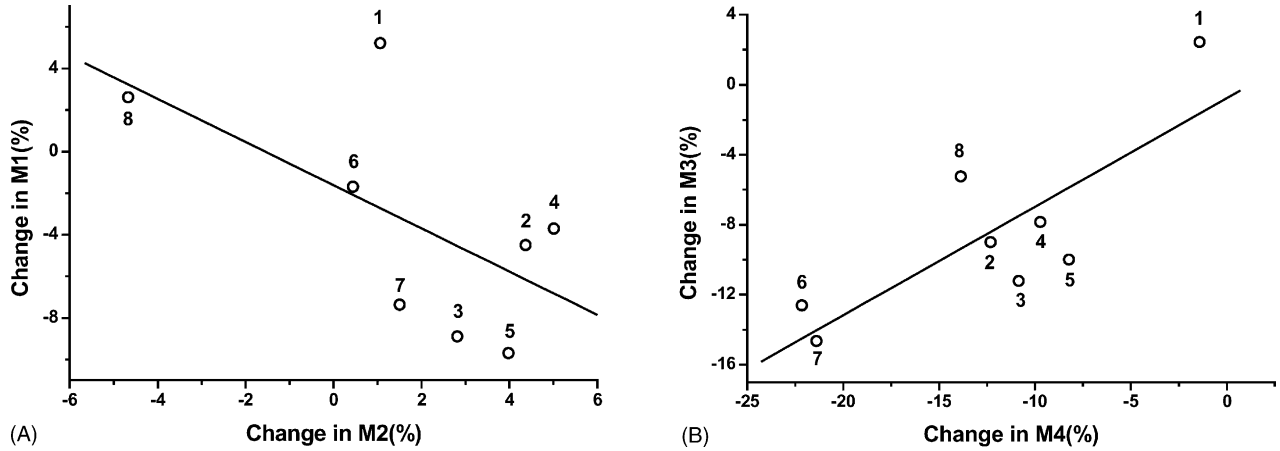

Fig. 2. Correlation of the changes of sleep parameters. Each data point in the figure represents the percentage of change in one sleep parameter. (1) Sleep efficiency; (2) SWS duration; (3) SWS percentage; (4) REM sleep duration; (5) REM sleep percentage; (6) eye movements duration; (7) eye movements percentage; (8) rapid eye movements to REM sleep ratio. Solid lines represent the regression line fitted through these data points. (A) The adult monkeys (M1 and M2) did not show any consistent change of sleep parameters after the lesions ($r = -0.60$, $P = 0.12$). (B) The change patterns of sleep parameters in the adolescent monkeys (M3 and M4) were positively correlated ($r = 0.80$, $P = 0.02$).

Previous functional brain-imaging studies demonstrated that the lateral prefrontal cortex, including the FEF, is inactivated during REM sleep [7,20]. The human subjects participated in those imaging studies are mostly beyond 20 years old. Thus, the negative results in the adult animals in our experiment is consistent with their findings, suggesting that the FEF is unlikely to be involved in the regulation of rapid eye movements during REM sleep in adult individuals. However, the design of the present study was not developed to totally exclude the possibility that the FEF plays a role in the control of the eye movements during REM sleep. In order to thoroughly investigate this subject, further study may compare the activities of the FEF in oculomotor tasks during wakefulness with that in the eye movements during REM sleep, or measure the spatial-temporal pattern of eye movements accurately during REM sleep before and after the FEF lesions.

In contrast with that in the adult monkeys, both the total time and percentage of rapid eye movements during REM sleep was decreased moderately after the FEF lesions in adolescent monkeys. Sleep may be influenced by several factors. In addition to the effects of the FEF lesions, the changes of sleep parameters we observed in adolescent animals might involve effects of adaptation to the experimental sleep recording environment and/or posttraumatic sleep disturbance caused by the surgical operation of lesions. However, the lesions affected neither the total sleep time nor the SWS, and we did not observe any time-dependent change of sleep parameters during a single recording session before or after the lesions (data not shown), suggesting that effects of adaptive factors on the present results should be minor. It is also unlikely that the posttraumatic factor had contributed much to the results. The postoperative sleep disturbance is characterized by a reduction in non-REM sleep and an increase in REM sleep [29]. But this is not the case for the current study. Therefore, we believe that the changes of the sleep parameters in adolescent monkeys are predominantly due to the effects of the FEF lesions. This result suggests that the FEF, although not be involved in the regulation of eye movements during REM sleep in adult monkeys, may has a different role in adolescent animals.

What, then, caused the distinct effects of the FEF lesions on adolescent and adult monkeys in the present study? Similar with the reasons discussed above, we can basically exclude the possibility that age-differential effects of adaptation and posttraumatic sleep disturbance have contributed much to the results we observed. Then, another factor emerges as a potential candidate, that is, the different developmental stages of the FEF in adolescent and adult animals. It is known that peak frontal development is reached around adolescence in humans [1,25,34]. Several studies have also observed the similar timetable of the frontal development in monkeys [9,16,28]. Thus, it is conceivable that the development of FEF, which is a part of the frontal cortex, also lasts into adolescence. Indeed, Munoz et al. found that the functions of FEF are not fully developed until about 20 years of age in humans [24]. Therefore, different degrees of FEF maturation between adolescent and adult monkeys probably provide the neurological correlates for the different effects of the FEF lesions in our observation. This hypothesis is consistent with the previous findings that oculomotor characteristics for REM sleep in infants are different from that in adults [18], which suggests that the mechanisms underlying the control of rapid eye movements during REM sleep undergo a developmental alteration after the birth. However, as a preliminary study, we may just provide a clue for further investigation on this issue. Why the lesions of the developing FEF can alter the sleep parameters while the same lesions of the fully developed FEF have no effects? Does REM sleep play a role in the development of the FEF, just as it

is involved in the development of some brain regions during the neonatal period (e.g., see Refs. [21,23] for review)? These questions are interesting candidates for future investigations.

In summary, the present experiment provides empirical evidence that the relation between the FEF and the regulation of the rapid eye movements during REM sleep is affected by age factor. Our result indicates that FEF is not related to the control of such eye movements in adult monkeys, whereas it may be related to it in adolescent monkeys. Thus, this finding also underscores the importance of age difference in future studies on both the functions of the FEF and the mechanisms underlying the regulation of the rapid eye movements during REM sleep.

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