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Clinical Study

The Effect of Sleep Deprivation on Ocular Vestibular Evoked Myogenic Potentials Using Air Conducted Sound

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Vestibular evoked myogenic potential (VEMP) in response to a loud air conducted sound (ACS) recorded from extraocular muscles, the so-called ocular VEMP (oVEMP), has been confirmed to be able to evaluate utricular function. This study aimed to evaluate the effect of sleep deprivation (SD) on oVEMP parameters. oVEMPs were recorded in 20 male healthy subjects once after an ordinary sleep and once after 26–29 h of SD. The latencies of peak N1 and P1, N1-P1 amplitude, N1-P1 interval, and asymmetry ratio (AR) of oVEMP recorded from both eyes under normal sleep and SD conditions were 10.04 ± 0.59 ms versus 10.56 ± 0.69 ms (left eye), 14.95 ± 0.92 ms versus 15.64 ± 1.05 ms (left eye), and 7.44 ± 2.86 μV versus 5.26 ± 2.15 μV (left eye); 10.08 ± 0.66 ms versus 10.64 ± 0.73 ms (right eye), 14.88 ± 0.89 ms versus 15.59 ± 1.02 ms (right eye), and 7.16 ± 2.88 μV versus 5.04 ± 2.05 μV(right eye); 10.40 ± 5.81% versus 11.43 ± 6.37%, respectively. After SD, the latencies of oVEMP were delayed and N1-P1 amplitude was lower, whereas N1-P1 interval and AR remained unchanged. The present study showed that oVEMP test could be used to evaluate the fatigue induced by SD.

1. Introduction

According to current US Army doctrine, aviation units may be required to operate around the clock during times of conflict. Continuous day-night operations provide obvious operational and tactical advantages on the battlefield [1]. Although aircraft can function for extended periods without adverse effects, human operators are susceptible to the influences of sleep deprivation (SD) and need periodic sleep for the restitution of both body and brain [2, 3].

Normal vestibular function is emphasized in the aviation medical literature as being a prerequisite for correct spatial orientation in flight [4]. However, the known effects of SD on vestibular function are less clearly defined. Some studies concern posturographic measurements after sleep loss: Uimonen et al. [5] showed that postural stability did not deteriorate after 24 h of sleep loss. Schlesinger et al. [6] found that while postural sway was not changed in response to SD, it increased when a secondary information processing task was associated. With regard to the vestibuloocular reflex (VOR) response, only three studies so far have described the effects of sleep loss on the VOR performance. Wolfe and Brown [7] firstly found no significant difference in VOR after 25–28 h of SD. Collins [8] also reported that the VOR velocity and duration remained unchanged after 24 h of SD and decreased from 48 to 52 h of SD. Quarck et al. [9] evaluated the effect of short total SD (26–29 h) on the horizontal VOR and more specifically on the horizontal canal-ocular responses. However, they found that sleep-deprived subjects displayed an increased slow-phase eye velocity of the VOR elicited by a velocity step and not by sinusoidal rotation. These studies are providing poor information on the effects of SD on the different aspects of vestibular function because they only evaluated the canal-ocular responses and did not investigate the effect of SD on otolith-ocular responses.

Vestibular end organs comprise three semicircular canals and two otolithic organs, that is, the saccule and utricle. Clinically, semicircular canal-ocular responses are assessed by the

caloric test with videonystagmography or rotational chair test, whereas safe simple tests of otolith function are not common [10]. Investigations by Todd et al. [11] demonstrated a short latency vestibular evoked potential with a negative peak at 10 ms (N10) and a positive peak around 15 ms (P15) in response to a loud air conducted sound (ACS) stimulus when recording from extraocular muscles, the so-called ocular VEMP (oVEMP), further research confirmed the oVEMP test can evaluate contralateral otolithic function via a crossed vestibuloocular reflex [12, 13].

Hence, the aim of our study was to provide a better insight into the consequence of short total SD (26–29 h) on the otolith-ocular reflex response. For this purpose, subjects performed an oVEMP test for evaluation of the utricular-ocular function after a night of normal sleep and after 26–29 h SD.

2. Materials and Methods

2.1. Subjects. We studied 20 male Chinese healthy volunteers (mean age 24.3 ± 2.4 years). None of the participants had any history of inner ear diseases or dizziness, hearing loss, or tinnitus. None of the subjects had habits of caffeine and alcohol drinking. The hearing level was normal in all participants according to ISO 7029 [14]. Horizontal head impulse, headshaking, vibration-induced nystagmus tests with Frenzel goggles, subjective visual vertical tests, and caloric tests were also within normal limits in all participants. The experiments were all performed in accordance with the Declaration of Helsinki and approved in advance by the Chinese Air Force Institute of Aviation Medicine Institutional Review Board. Each subject provided written informed consent before participation after all procedures had been fully explained.

2.2. Sleep Deprivation. Each subject performed the oVEMP test once after a standard night and once after a 26–29 h SD. A 2-week interval separated the oVEMP tests, with half the subjects starting with the SD and the other half with the control night. Subjects were studied in five groups of four each. They got up at 7:30 after 8 h good sleep and arrived for the experiment at 17:30 hours. A standardized supper was taken at 19:00 hours. Then two subjects (previously randomly selected) stayed in the laboratory while the two others went back home to sleep after they were asked to wear an actigraph to monitor their sleep duration. The subjects slept at home for the control nights because we wanted them to sleep as well as possible with no disturbances due to a different bed, noise, environment, and so forth. As the subjects were young and good sleepers, an actigraphic control of the night was appropriate: it has been shown that wrist actigraphy is a good indicator of sleep and wakefulness and is strongly correlated to polysomnography [15, 16]. Analysis of their actimetric profiles showed that all the subjects had normal sleep. During the night, they were not allowed to smoke, eat, or drink anything except water. At 7:30 hours the following morning, the two subjects who had slept at home returned to the laboratory and the four subjects had breakfast. The oVEMP tests were then conducted by a technician who was made blind as to the status of the subject between 10:00 hours and 12:30 hours. Each oVEMP test takes about two minutes.

2.3. oVEMP Test. The subjects were placed in a sitting position. Surface potentials, predominantly electromyographic (EMG) activities, were recorded (Smart EP 3.90, Intelligent Hearing Systems, Miami, FL). Two active electrodes were placed bilaterally around 1 cm below the center of the lower eyelid. The other two reference electrodes were, respectively, positioned about 1-2 cm below the active ones and one ground electrode was placed on the forehead. The electrode impedance was kept under 5 kΩ. During recording, the subjects were instructed and screened by a technician to look straight upward at a small fixed target more than 2 m away from the eyes, with a vertical visual angle of approximately 30° above horizontal.

Acoustic stimuli of 97 dB nHL (135 dB SPL) short tone bursts (STB) (500 Hz, rise/fall time = 1 ms, plateau time = 2 ms) with rarefaction polarity were delivered through ER3A-inserted earphones (Etymotic Research, Elk Grove Village, IL, USA). Stimuli were presented for 200 repetitions at a rate of about 5 Hz. EMG was amplified and bandpass filtered (10–1000 Hz), sampled at 10 kHz within 0 to 50 msec time window, and averaged. Bilateral oVEMPs were recorded simultaneously using binaural acoustic stimulation according to Wang et al. [17]. The oVEMP waveform was comprised of an initial negative peak (N1) with a mean latency of around 10 ms, followed by an initial positive peak (P1) with a mean latency of around 15 ms. Consecutive runs were performed to confirm the reproducibility of peak N1 and P1, which were interpreted by two independent reviewers to confirm that oVEMPs were present. Conversely, oVEMPs were absent when the biphasic waveform was not reproducible. The latencies of peak N1 and P1, N1-P1 interval, N1-P1 amplitude, and asymmetry ratio (AR) were measured. AR(%) was defined as the difference of the amplitude N1-P1 on each ear divided by the sum of amplitude N1-P1 of both ears, that is, [(larger amplitude−smaller amplitude)/(larger amplitude + smaller amplitude)] × 100.

2.4. Statistical Analysis. The parameters of the oVEMP such as latencies, interpeak intervals, amplitudes, and asymmetry ratio of ACS-oVEMP were expressed as mean ± SD and analyzed using SPSS (SPSS Inc., Chicago, IL, USA). We used a paired t-test to compare the parameters in the two conditions (SD and normal sleep). The level of significance was set at $P < 0.05$.

3. Results

All 20 subjects (40 eyes) had clear oVEMPs elicited by ACS in the two conditions. Figure 1 represents a typical oVEMP waveform for one subject after normal sleep and after SD. The latencies of peak N1 and P1, N1-P1 interval, N1-P1 amplitude, and asymmetry ratio (AR) in the two conditions (SD and normal sleep) were shown in Table 1. The latencies of peak N1 and P1, N1-P1 amplitude, and N1-P1 interval of oVEMP recorded in both eyes under normal sleep and SD conditions were 10.04 ± 0.59 ms versus 10.56 ± 0.69 ms (left eye), 14.95 ±

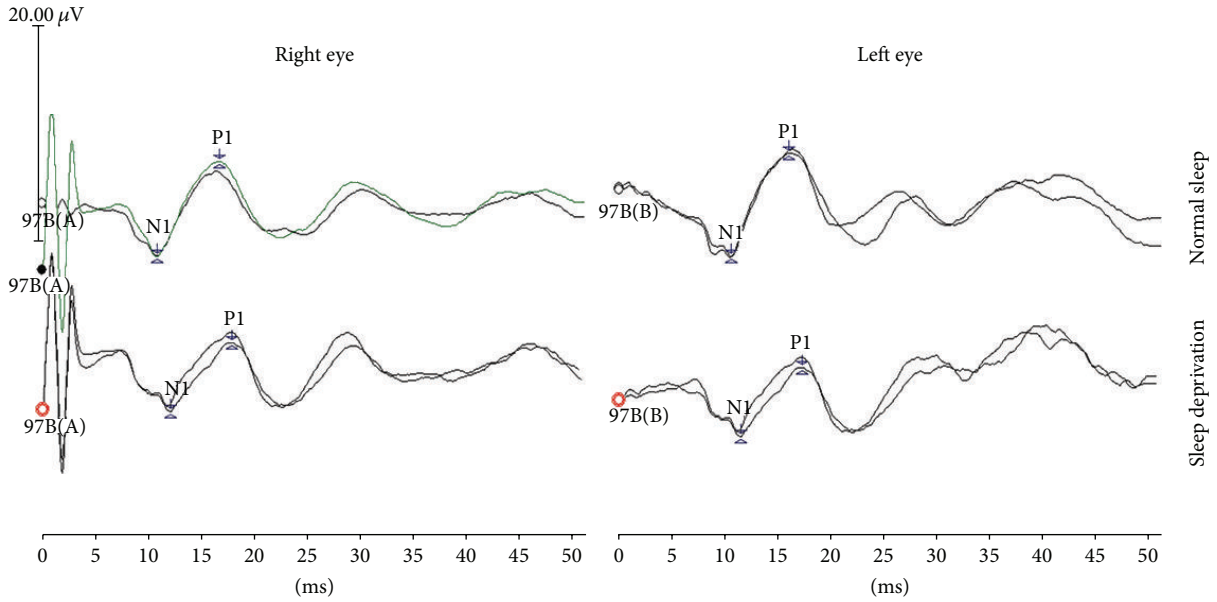

Figure 1: Example of oVEMP responses obtained by air-conducted shorted tone burst (500 Hz). Stimulation for one subject in two conditions (i) after one night of normal sleep or (ii) after one night of sleep deprivation.

0.92 ms versus 15.64 ± 1.05 ms (left eye), and 7.44 ± 2.86 μV versus 5.26 ± 2.15 μV (left eye) and 10.08 ± 0.66 ms versus 10.64 ± 0.73 ms (right eye), 14.88 ± 0.89 ms versus 15.59 ± 1.02 ms (right eye), and 7.16 ± 2.88 μV versus 5.04 ± 2.05 μV (right eye), respectively. AR of oVEMPs recorded under normal sleep and SD conditions was 10.40 ± 5.81% versus 11.43 ± 6.37%, respectively. After SD, the latencies of peak N1 and P1 were delayed and N1-P1 amplitude was lower ($P < 0.05$), whereas N1-P1 interval and AR remained unchanged.

4. Discussion and Conclusions

Our main finding is that sleep-deprived subjects displayed increased latencies of peak N1 and P1 as well as decreased N1-P1 amplitudes of oVEMP elicited by ACS.

We must take into account that the paradigm we have adopted, the control night spent at home, has produced several differences between the normal sleep and the sleep-deprived conditions. The first difference is obviously the sleep duration: it is crucial for the present study because we design it to compare subjects in normal sleep condition with subjects in sleep-deprived condition. But, since some environmental factors (temperature, hydration during the night, and travel between home and the lab) could have been different at home and in the laboratory, this paradigm could also have induced nonsleep-related differences between the two conditions. However, none of these environmental factors are known to change vestibular functions. Moreover, differences in environmental factors were minimal. Subjects ate nothing except water during the night and all meals before and after sleep or SD (supper and breakfast) were standardized meals. All the subjects lived near the laboratory (no longer than 10 min by walk), so there was no travel fatigue. All subjects, with or without SD, met up for breakfast at 7:30 hours the following morning while the experiment did not start until 10:00 hours, leaving a 2.5 h interval during which any effects that might have existed due to traveling in or different hydration levels had probably disappeared. Moreover Nguyen et al. [18] found that oVEMP latencies, amplitudes, and AR had excellent test-retest reliability (ICC > 0.75). Since oVEMP parameters are remarkably stable and thus only marginally influenced by environmental factors, thus, our finding that sleep-deprived subjects displayed delayed oVEMP latencies and decreased oVEMP amplitudes can be confidently attributed to SD.

oVEMP responses elicited by ACS are believed to originate from the otoliths and thus to contribute to the linear or translational vestibuloocular reflex [19]. The oVEMP test provides a way to evaluate the integrity of ascending vestibular pathways in the brainstem [20]. At the same time, the oVEMP, which is a surface electromyogram response beneath the eye, is likely to represent inferior oblique (IO) muscle activity. So the amplitude of oVEMP is influenced by the anatomical and physiological state of the extraocular muscles. For example, Sung et al. [21] ever found the gender difference in oVEMP amplitude and attributed it to variance in the muscle bulk between males and females. Behnke [22] found that 24 h SD can induce extraocular muscles muscular fatigue in the eye. Since the degree of upward gaze was kept constant in the present study, therefore the decrease of oVEMP amplitude may be attributed to the fatigue of extraocular muscle induced by SD.

Zils et al. [23] investigated the influence of SD on different types of saccadic eye movements. They showed that SD has a general impairing effect on the peak velocity of saccades, reflecting possible dysfunction at the level of the brainstem reticular formation.

It has been long known that SD can influence brainstem excitability by the change of synaptic plasticity and metabolism in brainstem. Pedrazzoli and Benedito [24]

Table 1: oVEMP parameters in normal sleep condition and sleep deprivation condition ($N = 20$).

Condition	N10 latency (ms)		P15 latency (ms)		N10–P15 interval (ms)		N10–P15 amplitude (μV)		Asymmetry ratio (%)
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	
Normal sleep	10.08 ± 0.66	10.04 ± 0.59	14.88 ± 0.89	14.95 ± 0.92	4.92 ± 0.91	5.08 ± 0.97	7.16 ± 2.88	7.44 ± 2.86	10.40 ± 5.81
Sleep deprivation	10.64 ± 0.73	10.56 ± 0.69	15.59 ± 1.02	15.64 ± 1.05	4.94 ± 1.04	5.02 ± 1.06	5.04 ± 2.05	5.26 ± 2.15	11.43 ± 6.37
t value	2.55	2.56	2.35	2.21	0.07	0.19	2.68	2.73	0.53
P value	0.02	0.01	0.02	0.03	0.95	0.85	0.01	0.01	0.60

found significant downregulation of beta-adrenergic receptors in the rat brainstem after SD. Mallick and Thakkar [25] showed that short-term SD might influence acetylcholinesterase in brainstem and they found that the acetylcholinesterase enzyme activity increased only in the rat medulla after 24 h SD. Thakkar and Mallick [26] compared monoamine oxidase, monoamine oxidase-A, and monoamine oxidase-B activities in sleep-deprived rat brain and they found that monoamine oxidase activity decreased significantly in the rat brainstem after SD. Mallick and Gulyani [27] observed that total calcium concentration increased in the rat brainstem after SD. Since it is known that calcium plays an important role in cellular functioning, these changes in calcium concentration may be the underlying mechanism for SD induced cellular expressions and behavior of neurons. Benedito and Camarini [28] showed that the increase in Achase activity induced by SD was specific to some upper brainstem regions in rat. These regions include the pons where cholinergic neurons are located and the medulla oblongata which receive cholinergic input from the pons. Ramanathan et al. [29] also noted that prolonged SD significantly decreased superoxide dismutase activity in the rat brainstem. Franco et al. [30] indicated that the depressed arousals that follow SD have been partly attributed to the disturbances within the reticular formation of the brainstem, which integrates specific facilitatory inputs, such as ascending pathways from vestibular receptors.

The changes of oVEMP parameters similar to our study have been found in migraine patients and aging subjects. Gozke et al. [31] found that, compared with healthy controls, mean latencies of N1 and P1 of oVEMP were significantly longer, while N1-P1 amplitudes of oVEMP were meaningfully lower in patients with migraine. Schuh-Hofer et al. [32] demonstrated a significant increase of brainstem brain serotonin transport protein (SERT) availability in migraineurs, suggesting a dysregulation of brainstem serotonergic system, which is located in the raphe nuclei and the adjacent reticular formation in the brainstem. The changes of oVEMP parameters in migraineurs may be related to it. Tseng et al. [33] investigated the effect of aging (>60 years old) on the oVEMP parameters and they found that the effect included prolonged N1 and P1 latencies and decreased N1-P1 amplitude. This effect may be related to the alterations in the morphology and maturation of brainstem reticular formation mechanisms induced by aging [34, 35].

Therefore, it is hypothesized that in our study the delay of oVEMP latencies and decreased oVEMP amplitude may be explained by SD induced dysfunction at the level of the brainstem and the fatigue of extraocular muscles.

The duration used in our study, 26–29 h, is one more commonly experienced by the general public (students, shift-workers, and jet-lag). It is therefore interesting to note that even this short-duration SD can have effects on the vestibular function and hence possibly on the subject's perception of body motion in space. It would therefore appear necessary to assess its impact in real-life operational situations involving the subject's orientation in relation to his/her surroundings, for example, when piloting an aircraft.

In conclusion, the present study showed that short-duration SD changed the otolith-ocular reflexes demonstrated by an increase in the latencies and a decrease in the amplitudes of oVEMP. It is proposed that the changes of oVEMP parameters after SD may be related to the dysfunction at the level of the brainstem and the fatigue of extraocular muscles induced by SD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Su-Jiang Xie and Hong-Zhe Bi contribute equally to this paper.

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