物，電話の使用などのより高次の生活機能であるinstrumental ADLがあり，この両者を評価する必要がある．LawtonとBrodyは高齢者の日常生活における自立度の簡便な評価尺度として，instrumental ADLに対してinstrumental activities of daily living scale（IADL）を，basic ADLに対してphysical self-maintenance scale（PSMS）を考案し，その有用性を示した[22)~24)]．

表2に日本語版IADL[25)]を示す．評価にあたっては，本人の日常生活をよく知る家族ないし主たる介護者から聴き取りを行う．IADLは8項目から構成されているが，対象が男性の場合には「食事の支度」「家事」「洗濯」については評価しない．したがって，得点範囲は男性では0～5点，女性では0～8点となる．PSMS[26)]（**表3**）は男女とも6つの基本的な生活機能を評価し，合計点を算出する．必ずしもIADLとPSMSの両者を評価する必要はなく，必要に応じていずれか一方のみの使用も可能である．

Ⅶ おわりに

神経心理学とは「高次精神活動を脳の構造との関連において研究する分野」であり，失語，失行，失認などの代表的巣症状のみならず器質性の幻覚，記憶障害，知能障害，情動障害をも対象としている[27)]．前述したように最も重要なことは検査を施行して点数を算出することではなく，診察や検査を通じてAD患者を含む対象者の症候を的確に把握し，記載することである．

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Neuroscience Letters
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Heart rate variability under acute simulated microgravity during daytime waking state and nocturnal sleep: Comparison of horizontal and 6° head-down bed rest

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Received 4 November 2004; received in revised form 28 March 2005; accepted 29 March 2005

Abstract

This study examined the acute effect of cephalad fluid shift under simulated microgravity on heart rate variability (HRV) during both daytime waking state and nocturnal sleep. Seven healthy male volunteers (21–31 years) underwent a series of experiments involving 6° head-down bed rest (HD) for 3 days. A control experiment on the same subjects was conducted under horizontal bed rest (HZ) in the same series. HRV from electrocardiogram signals was periodically calculated by the MemCalc method during daytime on the first and second days of both conditions. Nocturnal sleep on the first night of bed rest was monitored by polysomnography. HRV during stage 2 sleep and REM sleep were assessed in the former and latter halves of the sleep period time. Nocturnal sleep architecture under both conditions was normal, but a slight decrease in stage 4 sleep and an increase in the number of arousals occurred under HD. On both the first and second days, HRV during the daytime did not differ between HZ and HD. In contrast, high frequency components in HRV during sleep stage 2 were significantly higher in the latter half of sleep under HD than under HZ, although there were no differences in the ratio of low frequency to high frequency components during both stage 2 and the REM stage between the conditions. These results suggest that the acute effect of the cephalad fluid shift on cardiac autonomic nervous activity might be affected by the sleep/wake state modulating the dominance between sympathetic and parasympathetic nervous activity.

Keywords: 6° Head-down bed rest; Autonomic nervous activity; Sleep; Awake

Change in autonomic nervous activity in space is a well-known physiological process. This phenomenon is related to orthostatic intolerance in a considerable number of astronauts after they return to earth [3]. It is known to be mediated by the acute cephalad fluid shift, which induces hypovolemia; this, in turn, affects the reflex control of the cardiovascular system [19,20]. Specific changes in basal autonomic nervous activity have been reported under actual and simulated microgravity by direct measurements of muscle sympathetic nerve activity [10,18] and by employing indirect indices derived from heart rate and blood pressure [14,15,25].

The frequency domain analysis of heart rate variability (HRV), which is a non-invasive measurement for estimating cardiac autonomic tone with less distress to the subject [1,24], has been applied to various experiments in the field of space medicine. In these studies, decreased high frequency power (HF) of HRV in subjects who are awake, which suggests decreased vagal tone, has been demonstrated during and after actual [21] and simulated [6,14,15,25] microgravity exposure. Although it has been reported that HRV during sleep

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0304-3940/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2005.03.058

dramatically varies according to the sleep stage [9,29] and that it demonstrates clinical implications relevant to myocardial infarction [30], panic disorder [31], and insomnia [2], only one study has examined HRV in each stage of nocturnal sleep under microgravity [13]. In that study, the changes in HRV that occurred during sleep aboard the spaceship were not conclusive because of the individual differences among the subjects and, unfortunately, no result regarding autonomic nervous activity during daytime was presented. Therefore, it is unclear whether there are any differences in the responses in cardiac autonomic nervous activity under microgravity during the states of daytime waking and nocturnal sleep.

The purpose of the present study was to examine HRV under acute simulated microgravity during both daytime waking and nocturnal sleep. In order to sort the values of HRV according to sleep stage, polysomnographic sleep recording was conducted. To determine the effect of the cephalad fluid shift itself, two experimental runs with similar time schedules were conducted to compare HRV; one experiment involved 6° head-down bed rest (HD) for simulated microgravity, and the other experiment involved horizontal bed rest (HZ) as a control.

The experimental protocol was approved by the ethics committee of the National Space Development Agency of Japan. Seven healthy male volunteers (age, 26 ± 4.5 years; height, 173 ± 6.9 cm; weight, 70 ± 11.0 kg) participated in the study after receiving a thorough explanation of the protocol and providing written informed consent.

A series of experiments that involved 3 days of bed rest were conducted twice on the same subjects; one experiment involved an HD, and the other involved an HZ. A 5-day interval was set between each experimental run, and the order of HD or HZ was counterbalanced across the subjects. From 1 week before through to the end of the experiment, the subjects maintained a similar sleep schedule without a daytime nap; this schedule was confirmed by Actigraphic recordings [7].

The subjects came to the bed rest laboratory 2 days prior to the beginning of each bed rest experiment. The first 2 days in the laboratory were used as an ambulatory control period, wherein the subjects performed several familiarization sessions for the planned measurements during bed rest. On the third day, after breakfast and evacuation, the subjects started HZ at around 09:30. During the HD session, 20 min after the start of horizontal bed rest, the bed position was fixed at 6° head-down position until 18:00 on the fifth day. With regard to the HZ condition, the same experimental procedure was conducted, maintaining the horizontal bed position until the end of the bed rest period.

During the bed rest period, the subjects were requested to lie down on the bed in the position specified, except during evacuation, which they were requested to carry out within 15 min after breakfast. The scheduled time for sleep was from 00:00 to 08:00, during which room illumination was lowered to 10 lx. Napping was prohibited during the daytime (from 08:00 to 24:00) and the illumination measured at the level of the subjects' face was controlled at 1000 lx during this period. However, during the bed rest period, the subjects were allowed to read, talk, or watch television, which was placed at their bedside, when they had no scheduled experimental measurement. The subjects were continuously observed, either directly or by video monitoring, throughout the bed rest period to ensure that they did not take a nap or sit up during daytime. Breakfast, lunch, and dinner without spicy foodstuffs or caffeine were provided at 08:30, 13:00, and 19:30, respectively, while daily water intake was controlled at 20 ml/kg body weight per day. The subjects were requested to drink an equal amount of water every 2 h from 10:30 to 22:30.

After complete voiding at 08:00 on the day before bed rest, urine was collected until 24:00 on the second day of bed rest. Urine volume during the daytime (from 08:00 to 24:00; 16 h) and during the night (from 24:00 to 08:00; 8 h) was separately measured on each day.

Polysomnographic sleep monitoring was performed when the subjects stayed in the bed rest laboratory. Digital sleep recordings were performed with a Polymate system (TEAC, Tokyo, Japan) with electrode placements at C3, F3, and O1, left and right outer canthi, and submentally. The sleep recordings obtained on the first night under the bed rest condition were scored in 20-s epochs according to standardized scoring criteria [27].

Throughout the subjects' stay, the R–R intervals of the electrocardiogram were continuously monitored using an activetracer, model AC-301 (GMS, Tokyo, Japan) with a sampling rate of 1 kHz. Power spectrum analysis of HRV was performed by the MemCalc method [28] using a commercial software (MemCalc/Win, Suwa Trust, Tokyo, Japan), developed for analyzing data files transferred from an activetracer. Heart rate (HR) and the power spectrum bands consisting of high frequency (HF: 0.15–0.40 Hz) and low frequency (LF: 0.04–0.15 Hz) components [1] were computed every minute. HF, reflecting respiratory-induced cardiac sinus arrhythmias, was identified as an index of cardiac vagal activity [1,24]. The ratio of low frequency to high frequency components (LF/HF) was then calculated as an index of sympathovagal balance [1,24]. The data sampled after 18:30 on the second day of bed rest was rejected because measurements and treatments for the other purpose were started from 19:00.

Regarding data analysis during daytime, the average values of HR, HF, and LF/HF for 30 min were periodically calculated. The periods over which data was averaged, six times each on both the first and second days, are shown in Fig. 1. The 30-min period after meals was excluded from the data-averaging period. Due to scheduling constraints, the data-averaging period was reduced to 20 min after 08:05 on the second day of bed rest. Subjects maintained a supine position during these periods.

With regard to the data on the first night of bed rest, the values were sorted according to sleep stage. Since it has been reported that HF and LF/HF differ across sleep stages [9,29], we chose the values only when three consecutive 20-s sleep

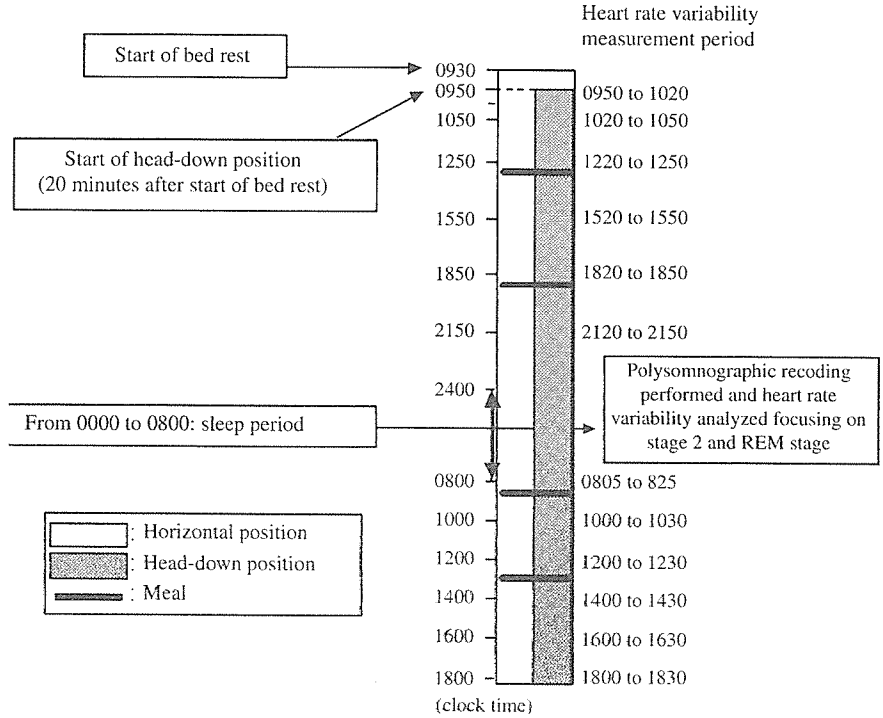

Fig. 1. Time schedule and heart rate variability measurement period for the first and the second days under each bed rest condition.

epochs were included in stage 2 and the REM stage, which commonly appears during both the early and the latter portions of the sleep period time (SPT). Based on these values, average values of HF and LF/HF during each of sleep stage 2 and the REM stage were calculated during the entire SPT and in the former and latter halves of the SPT, respectively.

All the values are expressed as mean ± S.E. A two-tailed paired *t*-test was used to compare urine volume and sleep parameters between HD and HZ. Analysis for HF and LF/HF during the daytime was separately conducted on both the first and the second days of bed rest by employing a two-way ANOVA (bed rest condition × time) for repeated measures. Average values of HF and LF/HF during each of sleep stage 2 and the REM stage obtained during the entire SPT and in the former and latter halves of the SPT were compared between HD and HZ using the Wilcoxon matched-pairs signed-ranks test. Statistical significance was defined as $P < 0.05$.

Urine volume during daytime was observed to increase on the first day under both bed rest conditions (HZ: 2127 ± 112 ml; HD: 2039 ± 125 ml) as compared to conditions prior to bed rest (HZ: 1111 ± 78 ml; HD: 1497 ± 195 ml) and on the second day of bed rest (HZ: 1331 ± 101 ml; HD: 1419 ± 149 ml). However, no significant difference in urine volume was observed between HZ and HD.

Sleep parameters measured on the first night of bed rest are shown in Table 1. Sleep parameters calculated for the entire

Table 1
Comparison of sleep parameters between horizontal and 6° head-down bed rest

	Results over entire TIB		Former half of SPT		Latter half of SPT	
	HZ	HD	HZ	HD	HZ	HD
TST (min)	441.5 ± 6.9	444.1 ± 3.0	223.7 ± 4.2	225.1 ± 3.0	222.5 ± 3.1	222.2 ± 2.5
SEI (%)	92.0 ± 1.4	92.6 ± 0.6	–	–	–	–
Sleep latency (min)	18.1 ± 6.5	11.4 ± 2.9	–	–	–	–
Stage REM (%)	26.8 ± 4.9	21.1 ± 2.0	17.6 ± 1.8	17.3 ± 2.2	27.6 ± 2.6	24.9 ± 3.3
Stage 1 (%)	14.0 ± 2.2	15.3 ± 1.6	11.4 ± 1.5	15.2 ± 1.7	164 ± 3.1	15.4 ± 2.3
Stage 2 (%)	46.5 ± 4. 7	47.9 ± 3.6	45.5 ± 4.9	44.8 ± 5.5	47.2 ± 4.5	50.9 ± 2.2
Stage 3 (%)	9.4 ± 1.1	8.7 ± 0.9	14.5 ± 1.5	14.6 ± 1.8	4.1 ± 1.4	2. 8 ± 1.1
Stage 4 (%)	3.6 ± 1.1	2.0 ± 0.7*	7.0 ± 2.1	3.7 ± 1.4*	0.2 ± 0.2	0.2 ± 0.1
WASO (%)	3.4 ± 0.9	4.5 ± 0.4	3.2 ± 1.0	3.9 ± 0.8	3. 6 ± 1. 2	5.1 ± 1.3
MT (%)	1.0 ± 0.3	0.6 ± 0.2	0.9 ± 0.3	0.5 ± 0.2	0.9 ± 0.4	0.6 ± 0.2
Number of arousals	21.7 ± 3.9	30.7 ± 3.3*	8.9 ± 1.5	14.4 ± 1.7	12.9 ± 2.9	16.3 ± 3.0

Values are expressed as mean ± S.E. TIB: Time in bed; SPT: sleep period time; TST: total sleep time; SEI: sleep efficiency index; WASO: wake after sleep onset; MT: movement time; HZ: horizontal bed rest; HD; 6° head-down bed rest.
* $P < 0.05$.

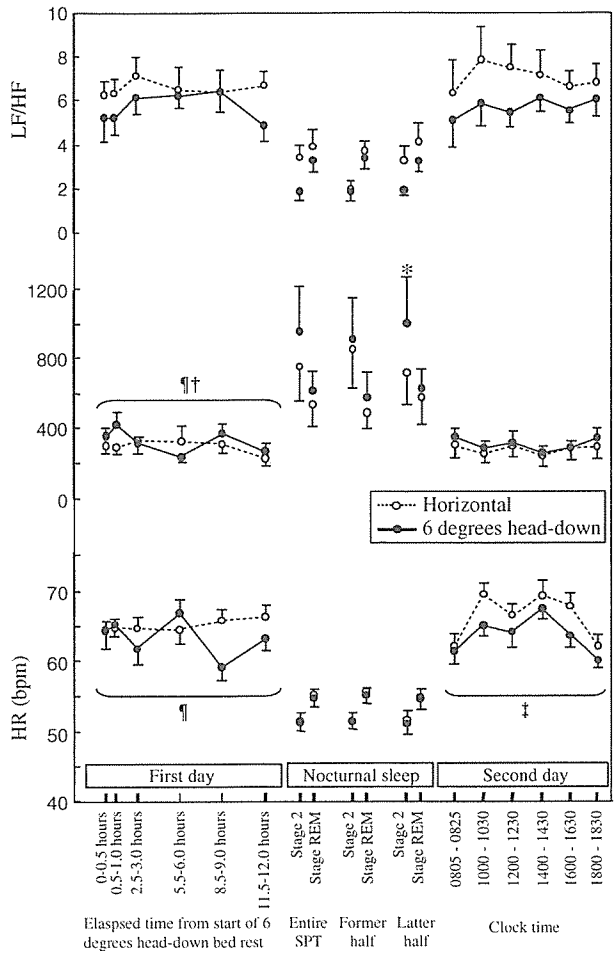

Fig. 2. Changes in HR, HF, and LF/HF during the initial 2 days under both bed rest conditions, including values during stage 2 and REM stage in former and latter halves of sleep period time. *: $P<0.05$ using Wilcoxon matched-pairs signed-ranks test; ¶: significant interaction of time × bed rest condition ($P<0.05$) using repeated measure ANOVA; †: significant effect of time ($P<0.01$) using repeated measure ANOVA; ‡: significant effect of time ($P<0.001$) using repeated measure ANOVA.

night showed no significant difference between HZ and HD, except for a slight but significant decrease in the percentage of stage 4 sleep and an increase in the number of arousals under HD. In each of the former half and latter halves of SPT, although there was no significant difference in the sleep parameters in the latter half, the percentage of stage 4 sleep in the former half was significantly lower under HD than that under HZ.

The values of HR, HF, and LF/HF throughout the initial 2 days of bed rest, including the data sampled during stage 2 sleep and the REM stage on the first night, are illustrated in Fig. 2. Under both bed rest conditions, the values of HF were apparently higher during nocturnal sleep, whereas the values of HR and LF/HF were apparently higher during daytime periods when subjects were awake. There was no significant effect of time and bed rest condition on HF and LF/HF during the daytime, except for HF on the first day, which revealed a significant effect of time ($F(1,5)=3.468$, $P<0.01$), and an interaction of time with bed rest condition ($F(1,5)=3.088$, $P<0.05$). On the first day, the values of HR under HD showed a larger fluctuation compared to those under HZ, and a significant interaction of time × bed rest condition ($F(1,5)=2.529$, $P<0.05$) was detected. On the second day, the values of HR under both bed rest conditions changed similarly through the daytime. These HR values showed lower values at 08:05 and 18:00, and a significant effect of time ($F(1,5)=11.498$, $P<0.001$) was detected.

During the entire SPT, although LF/HF did not show any statistical differences during both stage 2 sleep and the REM stage, HF during stage 2 sleep showed a tendency to increase under HD than under HZ ($P=0.063$). In the former half of SPT, HF and LF/HF during both stage 2 sleep and the REM stage showed no difference between the bed rest conditions. On the other hand, HF increased significantly ($P<0.05$) in the latter half of the SPT; LF/HF tended to decrease ($P=0.091$) during stage 2 sleep under HD as compared to under HZ. No difference in HF and LF/HF was observed during the REM stage in the latter half of the SPT. There was no difference in HR between the two conditions during both sleep stages during any period of the night.

The present study is the first report to examine HRV during both the daytime waking state and polysomnographically determined nocturnal sleep under microgravity. The primary findings of this study are that the difference in HRV between HZ and HD, as a sole effect of the acute cephalad fluid shift, was an increased HF during stage 2 NREM sleep under HD, but not during REM sleep and the daytime waking state. Previous studies have demonstrated that HF during the daytime waking state consistently decreased after long-term exposure to simulated or actual microgravity in cases of 14 and 15 days of 6° head-down bed rest [6,14,15] and 16 days of space flight [21]. In contrast, the results of acute responses in HRV within 2 days under 6° head-down bed rest have been reported to be inconsistent [14,15,17,25]. The present daytime findings were in agreement with the reports demonstrating unchanged HF under acute simulated microgravity [14,17]. As a larger fluctuation in HR observed on the first day under HD might reflect possible changes in cardiac autonomic activity induced by cephalad fluid shift, HRV under acute microgravity does not appear to be definitive.

As it has been shown that respiration has a major influence on HRV [16], Migeotte et al. [21] confirmed that the influence of respiration on HRV under actual microgravity was similar to that observed in a supine position on earth. In the present study, we made no attempt to artificially control the subjects' respiration when HRV was analyzed. However, Prisk et al. [26] reported that the respiration rate in wake subjects in the horizontal supine position and during 6° head-down bed rest was similar. Regarding the respiration rate during nocturnal sleep, although there has been no study to examine the effect of positional difference, it has been reported that the variations in respiration rate during nocturnal sleep are within a small range, which is unlikely to affect HRV [29]. Therefore, we could not assume any specific influence of respiration

on HRV values between HZ and HD during either daytime waking or nocturnal sleep.

Previous reports examining sleep architecture during actual space missions [8,23] or during 6° head-down bed rest [22] have demonstrated disturbed sleep characterized by poor subjective sleep quality, decreased total sleep time, and an increase in intermittent awakenings. As these studies examined nocturnal sleep several days after the onset of microgravity exposure, the present study is the first report to evaluate sleep architecture on the first night of 6° head-down bed rest. In contrast to previous reports, sleep architecture on the first night under HD was identified as being normal [5], despite a slight decrease in stage 4 sleep and an increase in the number of arousals. Since we carefully controlled the experimental environment (light/dark cycle, illumination, and food and water intake) and the subjects' behavior (no daytime nap under bed rest conditions and stable sleep/wake schedule during the experimental period), the present results suggest that 6° head-down bed rest itself has only a little effect on nocturnal sleep on the first night of bed rest.

The only comparable study evaluating HRV in each sleep stage was conducted on four astronauts aboard the Russian Mir space station [13]. In that study, although no significant effect of space flight on HRV was observed, an increase in HF during NREM sleep under microgravity was suggested by the statistical analysis, which incorporated their pre-flight resting HR as a covariate factor. The present study evaluated HRV during both the daytime waking state and nocturnal sleep under 6° head-down bed rest, and a significant increase in HF during stage 2 sleep was observed in the latter half of SPT, which was in line with the results described above [13]. The results suggest that changes in HRV under acute microgravity might be affected by the sleep/wake state. As can be seen in Fig. 2, which shows higher HR and LF/HF during daytime and higher HF during nocturnal sleep, cardiac autonomic nervous activity is sympathetic dominant during the daytime and vagal dominant during nocturnal sleep [11]. During these characteristic changes in cardiac autonomic nervous activity, the acute effects of the cephalad fluid shift might appear as increased HF during stage 2 sleep when the basal vagal tone is higher than that during daytime waking state and REM sleep [9,11,29]. Interestingly, a significant increase in HF under HD was observed only in the latter half of SPT. The reason for no significant increase in HF under HD in the former half of SPT was unclear. As acute responses in HRV under 6° head-down bed rest have been reported to be inconsistent in wake subjects [14,15,17,25], a possible interaction of elapsed time from the start of bed rest with the effect of the sleep/wake state might have induced the present results.

In spite of a significant increase in HF during stage 2 sleep under HD, HR showed no difference between HZ and HD. As HR is recognized as the net results of opposing sympathetic and vagal activities on the sinus node [12], these two autonomic activities during sleep were suggested to vary somewhat independently [4]. In fact, HR was reported to significantly correlate with LF/HF, but not with HF, during nocturnal sleep in healthy young subjects [4]. Therefore, although increased vagal activity during stage 2 sleep under HD could be suggested, the net results of sympathovagal balance, which are shown by HR and LF/HF, did not differ between HZ and HD.

In conclusion, nocturnal sleep architecture measured on the first night of bed rest was within the normal range in the 6° head-down position. In response to acute simulated microgravity exposure, the difference in HRV between HZ and HD was observed as an increase in HF during stage 2 sleep under HD, but not during REM sleep and the daytime waking state. These results suggest that the acute effect of microgravity on autonomic nervous activity might be influenced by its basal activity level modulated according to the sleep/wake state. In the case of actual space flight, other factors such as space motion sickness, excitement, and/or disturbed sleep may possibly act on the basal alteration of autonomic nervous activity induced by the cephalad fluid shift.

Acknowledgments

This study was carried out as a part of "Ground-based Research Announcement for Space Utilization" promoted by the Japan Space Forum. We greatly appreciate the valuable technical support and safety advice provided by Masamichi Sudo, Takuma Tozawa, Hiroyoshi Adachi, Nakamori Suganuma, Yasuhiro Sagami, and Yukio Ono.

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Question
快適睡眠の工夫は？

快適睡眠の工夫について教えてください．

Answer

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睡眠は複雑系の生命現象です．また，日常的な現象であり，生理的・心理的な影響を受けやすく，生活習慣によって大きく左右される側面をもつ現象です．快適睡眠確保のための基本的な工夫は，生活スタイルと睡眠環境の改善です．現在のところ理想的な睡眠薬は開発されておらず，薬剤により快適な睡眠が確保できるものではありません．睡眠は一生を通じての生命現象であり，睡眠健康の障害は心身の健康全般，脳機能，循環器系・免疫系機能，消化・代謝系機能，運動系機能の健全な働きを障害することもよく知られています．特に，人間の睡眠は，極度に発達した前頭葉機能を維持するために進化してきた特性をもっています．

快適な睡眠確保のための生活スタイルと睡眠環境の改善技術は，4分野に大別できます．不適切な要因が認められればその改善をはかります．分野別に，これまでの睡眠科学が明らかにした改善方策をそれぞれ列挙します．なお，生活スタイルの改善は習慣化が重要であり，中・長期的な視点で計画的に行うことが望ましいのです．

A）サーカディアンリズムの規則性の確保

サーカディアンリズムの規則性の改善は，快適睡眠確保のための第1にあげられる重要事項です．睡眠がサーカディアンリズムに強く影響されるという科学的事実は，多くの研究により明らかとなっています．

サーカディアンリズム

(1) 規則的な睡眠スケジュールと規則正しい食生活を守る．
(2) 軽度の有酸素運動を一定時間に行う．
(3) 朝，起床後2時間以内に太陽の光を30分以上あびる．

B）日中や就床前の良好な覚醒状態の確保

睡眠は覚醒と常に相互補完的な関係にあり，良質な覚醒は快適な睡眠を確保するための必要事項です．望ましい就床時刻に近い時点でのうたた寝や居眠りの混入は，主睡眠の入眠を妨害し，維持・安定性を障害します．また，日中の光環境が不十分な場合には，夜間メラトニン分泌が少なく，睡眠の維持を障害

「肥満と糖尿病」Vol. 4 No. 3 2005−521

その他

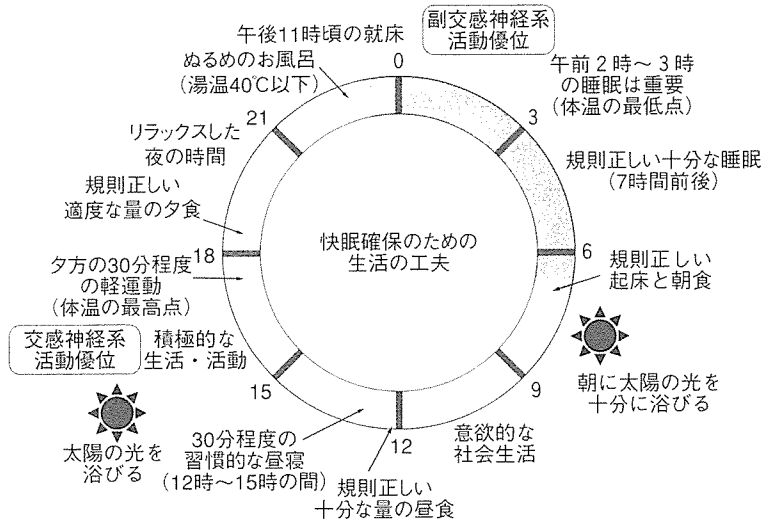

図　快眠確保のための生活上の工夫

しやすいことも判明しています.

(1)　日中はできるだけ意欲的な生活をこころがける.

(2)　高齢者では，習慣的入眠時刻から15時間前後に30分程度の短時間の昼寝をとる.

(3)　夕方に，30分程度の軽運動を行う習慣をもつ.

(4)　夕食後は，居眠りをしたり仮眠をとることは避ける.

(5)　日中に1時間以上，外光をあびる.

C) 良好な睡眠環境の整備

良好な睡眠環境の選定基準の詳細については他誌を参照されたいが，原則は下記の2点に集約されます.

(1)　自分にあった寝具を選ぶ.

(2)　静かで暗く適度な室温，湿度の寝室環境を維持する.

D) 就床前のリラックスと睡眠への脳の準備

脳が興奮した状態，交感神経系活動が亢進した状態，深部体温の低下が不十分な状態では，円滑な入眠が阻害されやすいことが知られています.

(1)　就寝間近のお茶や多量のアルコールなどの摂取や喫煙を避ける.

(2)　就寝間近の激しい運動や心身を興奮させるものは避ける.

(3) 就寝間近に熱いお風呂に入ることは避ける.

(4) 就寝1～2時間前より500ルクス以上の光環境を避ける.

(5) 眠れない場合には,無理に眠ろうとしない.

睡眠健康増進に関する研究で,ほぼ良好な結果の得られている事実を一日の生活習慣のなかに取り込み,とりまとめたものを図に示します.この図に示した生活習慣の調整法は高齢者を想定したものですが,若年者,中高年者でも原則はかわりません.毎日必ずすべてのものを行う必要はなく,可能なものから,週3回程度行っていくことで,快適な睡眠を確保するために有効な生活習慣を持続できます.

サーカディアンリズム(circadian rhythm):　人間の生命現象は脳内視床下部の視交叉上核に存在する生物時計により,約24時間の周期で変動している.睡眠・覚醒リズムも生物時計の支配下にあり,サーカディアンリズムの不規則性が睡眠を悪化させる例も知られている.

悪化した睡眠は一朝一夕に改善できるものではありません.睡眠に関する知識が不十分な場合には,睡眠にとって有用な生活習慣を教示し,生活習慣の改善については,4～8週間の計画の中で,睡眠障害の症状の改善状態を評価しながら行うことが大切です.

特集
夜間頻尿

睡眠障害と夜間頻尿

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Key Words　睡眠障害，夜間頻尿，高齢者，妊産婦，QOL

睡眠障害は健康被害をもたらし，加齢とともにその発生率が増加する．日常生活を障害する長期不眠は，高齢者では15％以上と見込まれ，高齢者のQOLを阻害する重要な要因である．睡眠障害の原因として，睡眠機能の低下，サーカディアンリズムの異常，身体・精神・神経疾患，生活習慣などが指摘されているが，夜間頻尿に関してはこれまであまり注目されていない．また，高齢者以外にも夜間頻尿により睡眠が障害される場面は，妊娠末期や更年期でも頻発する．本文では，夜間頻尿と睡眠障害との関係について概説する．

I　睡眠と健康

睡眠障害の健康に対する被害について，近年急速に研究が進んできている．また，睡眠障害のみでなく睡眠時間の不足も，健康を障害する可能性が指摘されている．100万人以上を対象としたKripkeら[1)]のコホート研究の結果では，6時間30分未満あるいは8時間以上の睡眠時間の者では健康被害のリスクが有意に増大している．また，不眠患者の50％が，12カ月以内に睡眠障害以外の何らかの医療的治療にかかっていることも，WHOの国際共同研究[2)]で確認されている．

睡眠が障害された場合に生じる個々の健康被害についても，かなりよく研究されている．睡眠障害により，免疫機能は減弱し，生体防御や生体維持機能が低下[3)]すると考えられている．循環器機能には，さらに深刻な影響が生じる．睡眠時呼吸障害は，高血圧症，右心室肥大，不整脈，多血症などの原因となり，虚血性心疾患や脳血管性痴呆の重要な要因となることが指摘[4)]されている．

痴呆等と直接的に関連する認知機能と睡眠との関係も，近年研究が盛んである．睡眠障害や睡眠

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不足は，注意（attention）を強く障害することが，多くの報告[5-8]から明らかとなっている．また，眠気は脳内の情報処理過程にも影響を及ぼす．睡眠不足より脳内情報処理に対応して出現する事象関連電位の1つであるP300の潜時が延長し注意の指標である振幅が減少し[9]，睡眠時呼吸障害による夜間睡眠の分断が，覚醒時の前頭葉，側頭葉，頭頂葉において，注意機能の指標であるP300の振幅を減衰[10]させる．

特に高齢者では，睡眠の障害あるいは不足は，認知機能の悪化に強く影響している可能性が高い．Asadaらは，アルツハイマー型痴呆患者の発症の危険因子について疫学的に検討し，60分未満の昼寝習慣をもつ者は危険率が有意に低下することを報告[11]しており，睡眠習慣や睡眠障害とアルツハイマー型痴呆発症との間に何らかの関連のあることも推定されている．

睡眠障害や睡眠不足は，学習や記憶にも影響する．夜間睡眠が分断され日中に強い眠気の混入する睡眠時呼吸障害の患者では，記憶が障害されるとする報告[12]は多い．また，1,000名の米国民を対象としたランダムサンプリングによる調査で，対象者を短期不眠，長期不眠および非不眠に分類し日中の状態を比較した研究では，不眠者で記憶，集中力，課題遂行力や人間関係を楽しむ能力に障害がみられたことが報告[13]されている．また，睡眠障害と記憶の関係では，ベンゾジアゼピン系，非ベンゾジアゼピン系を問わず，睡眠導入剤の副作用として記憶障害の存在することがよく知られている[14]．睡眠の分断や不足はREM睡眠を減少させる．REM睡眠は，記憶の固定過程に関与している可能性が高く[15-18]，学習能力の衰退との関連も疑われている．

前頭連合野のより高次な脳機能と睡眠との関係は，若年者に36時間の断眠を行わせた場合に，短期記憶テストの正解に対する自信度や連想記憶の想起能力が，高齢者のスコアまで低下するとする報告[19]，高齢不眠では，社会に対する協調性の低下や自己の生活に関する満足度などの意欲が低下するという筆者らの報告[20]などがある．

21～75歳の男女212名を対象に，ピッツバーグ睡眠質問票（PSQI）[21]とSF-36[22]を用いて睡眠障害とQOLとの関係を検討した筆者らの結果を図1に示す．PSQIの11点以上は睡眠障害の疑いが高いと判断され，11点以上と11点未満の2群でQOLを比較した．SF-36によるQOLは，身体健康と精神健康のサマリースコアに類別され，両者ともPSQIが11点以上の睡眠障害の疑いのある群で有意に悪化していた．このように睡眠障害は，身体，精神両面の健康に関連したQOLを障害し，生活に支障をもたらす原因となる．

睡眠障害の治療として，睡眠薬の投与でことたれりとする治療方針は，認知機能への悪影響の面から考えれば誤りである．大多数の睡眠薬は，認知機能に何らかの悪影響を及ぼすとともに，長期にわたる服用は健康を障害する可能性も疑われている[1]．睡眠障害の治療場面では，必要に応じての睡眠薬の適切な投与とともに，認知・行動療法などの睡眠衛生あるいは生活習慣の調整技術が有用な場合が多い[23]．

Ⅱ　夜間頻尿と睡眠障害

夜間頻尿は，単に高齢者の問題ではない．図2は，558名の18～45歳の非妊娠，妊娠女性の夜間排尿回数を比較した結果である．この年齢層の非妊婦では，わずか3.1％の女性が夜間入眠後に2回以上排尿があるのに対して妊婦では妊娠初期で23.6％，妊娠中期で32.7％，妊娠末期で

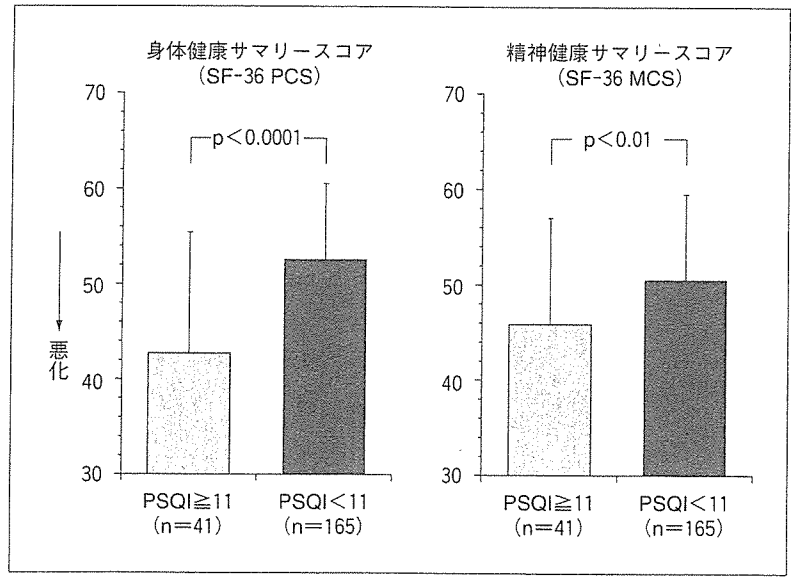

図1　睡眠障害によるQOLの障害

ピッツバーグ睡眠質問票（PSQI）得点が11点以上の睡眠障害者では，SF-36による身体健康と精神健康のサマリースコアが有意に悪化しQOLが障害されている．

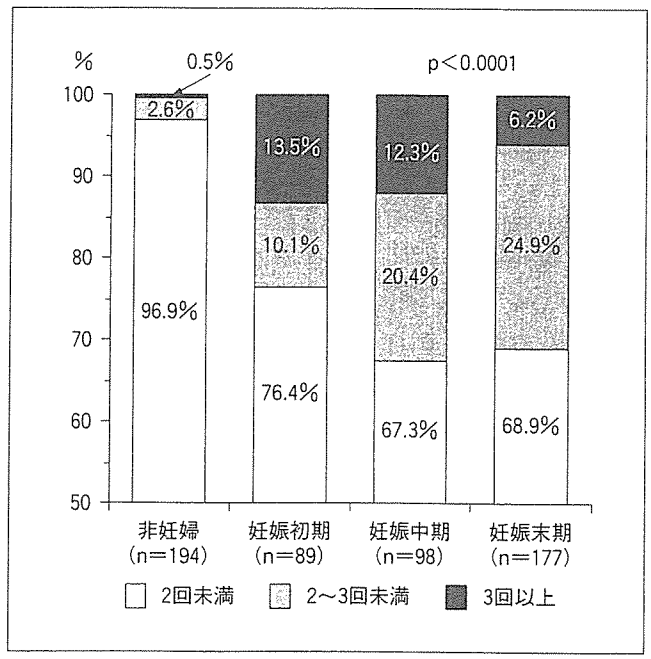

図2　非妊婦と妊婦における夜間排尿回数の差異

非妊婦に比べ妊婦では，夜間排尿回数の多い者が有意に妊娠初期から増加する．

31.1％と極端に増加する．妊娠初期でも明らかに高い夜間排尿回数を示し，この原因が胎児による膀胱の圧迫ではないことが明瞭である．体液循環量の増加，尿濃縮やナトリウム保持などの腎機能の変化，膀胱機能の変化，利尿ホルモンの分泌促進，抗利尿ホルモンのサーカディアンリズム異常などが考えられるが原因は不明である．この対象群での睡眠維持の障害は妊娠中期の群で最も強く，次いで末期，初期の順である[24]．このように妊婦においても夜間頻尿が睡眠障害に関係している可能性は高い．

東京圏の一般高齢住民192名を対象として，長期不眠の発症リスク検索を行った筆者らの調査[25]では，睡眠維持の障害に対する夜間頻尿の寄与率は0.447と思った以上に高く，高齢者に多い不適切な生活習慣を大きく上回っていた．疾患発症要因の検索で得られる値としては，これまで知られているものの中でも際だって高い値である．高齢者の場合，実質的な排尿の必要がない場合でも，夜間睡眠が障害され中途覚醒後に膀胱内圧が軽度でも高まっているとトイレに行くことが知られている．このような夜間頻尿は，睡眠障害が主たる原因であるが，排尿障害が中途覚醒の頻度を増大させることを自身が体験しているため，このような状況が生じやすい．中途覚醒後に，排尿に行かず再入眠する場合と，排尿に行き再入眠する場合では，行動覚醒による睡眠の中断，トイレでの光環境による覚醒効果，冬などは室温の低下による寒冷刺激など，再入眠を困難とする要因が，排尿行動には含まれている．このようなさまざまな要因の含まれる夜間頻尿が，高齢者の熟眠不全や中途覚醒を主訴とする長期不眠に関与している可能性は高い．

癌・循環器疾患の発症率が低く健康余命を誇る沖縄では，東京圏と比べ睡眠障害愁訴率は低いが，それでも高齢者の10％弱に長期不眠が認められた．筆者らが那覇市近郊で行った60～99歳の男女732名を対象とした睡眠健康に関する調査で，60歳代で7.1％，70歳代で9.9％，80歳以上では17.6％の者が1カ月以上持続する不眠を訴えていた．これらの長期不眠の多くは，入眠困難を主訴とするものでなく，中途覚醒等による睡眠維持の障害が主たる病像であった．

上記沖縄在住の高齢者での睡眠中の中途覚醒頻度と夜間排尿回数の関係を**図3左**に示す．**図3左**は，一カ月平均の夜間排尿回数と中途覚醒頻度との関係を散布図と回帰直線で示したものである．夜間頻尿のある高齢者は，明らかに中途覚醒が増加している．両者の相関は，$r = 0.7208$ ($p < 0.0001$) と非常に高い．夜間排尿回数が3回未満の者の中途覚醒頻度のばらつきは大きいが，3回以上の夜間排尿回数を示す者では，中途覚醒頻度との関係がほぼ一線上に分布している．

一晩に2回未満，2回以上3回未満，3回以上の者の割合を，長期不眠者とそれ以外の者で**図3右**に示す．長期不眠者では，23.8％の者が3回以上の夜間睡眠中の排尿回数を示すのに対し，長期不眠をもたない者では8.8％であった．一般に，2回以上の中途覚醒が存在する者では不眠愁訴の多いことが，経験的に知られている．そこで2回以上の夜間排尿回数を示す者の割合を両群で比べてみると，長期不眠者では55.6％と半数以上であるが，長期不眠をもたない者では29.4％と両群には明らかな差 ($p < 0.0001$) が認められている．この対象群では，性差や肥満度で夜間排尿回数に差は認められていない．また，長期不眠の発症頻度にも性差や肥満度で差は認められない．これらのことは，高齢者の長期不眠の発症に夜間頻尿が相当な比重を占めている可能性の高いことを示唆している．

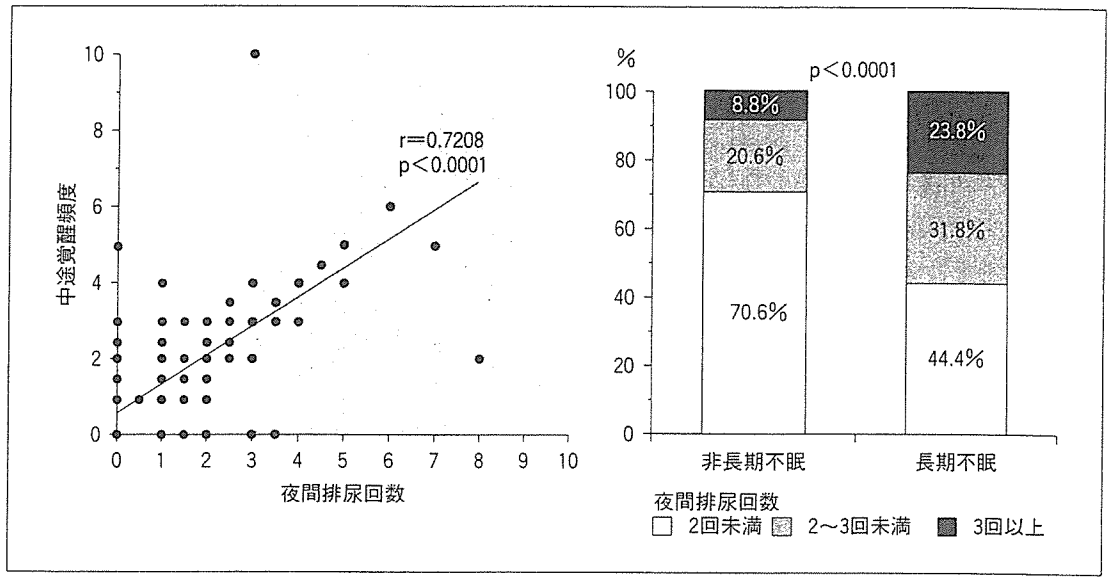

図3　夜間排尿回数と中途覚醒頻度との関係

沖縄在住男女732名（女性418名，男性314名，60～99歳）の夜間排尿回数と中途覚醒頻度との関係を図左に散布図で示す．夜間頻尿のある者では，明らかに中途覚醒が増加する．両者は，r＝0.7208と非常に高い相関を示す．図右に，長期不眠者と非長期不眠者での夜間排尿回数頻度の割合を示す．長期不眠愁訴をもつ者では，有意に夜間排尿回数が多い．

夜間排尿回数と中途覚醒頻度は，加齢とともに増加する．60歳代では，夜間排尿回数は平均で1.0回，中途覚醒は1.3回であるが，70歳代ではそれぞれ1.4回と1.5回に増える．さらに80歳を超えると夜間排尿回数は2.1回と平均で2回を超え，中途覚醒頻度も2.3回となっていた．特に問題となりやすい夜間排尿3回以上の者は，60歳代では約5％であるが70歳代で11％となり，80歳を超えると32％にもなる．同時に，長期不眠愁訴も7％，10％だったものが80歳を超えると18％にも増加していた．加齢とともに夜間排尿3回以上の者が増え，それに伴って長期不眠愁訴が増大し，両者の加齢による増加パターンは，相当に類似し高齢者では夜間頻尿が長期不眠を引き起こしている可能性が高い．

高齢者において長期不眠と夜間頻尿は，表裏一体の関係にあることが多い．睡眠が質的に悪化し中途覚醒が増えるので二次的に夜間頻尿となるケースも多々存在する．一方で，前立腺肥大のような泌尿器疾患により夜間頻尿が生じ，それが睡眠維持障害を引き起こす場合[26]もある．また，高齢者の2％以上に，腎透析患者では20～30％にみられるむずむず脚症候群[27]のような特異な睡眠障害が，夜間頻尿を併発している場合もある．さらに，抗利尿ホルモンの日内変動の異常が，サーカディアンリズム異常により引き起こされている症例も存在すると推定されている．さまざまな要因が夜間の排尿回数と排尿量を増加させ睡眠を障害するが，その多くは一日排尿量には差異はみられないとの報告[28]もあり，治療指針を策定するうえでも，日中と夜間の排尿量配分の検査は重要な指標となりうる．

中高年女性を対象とした調査であるが，運動習慣を有する女性では入眠後の排尿回数が少ないと

いう結果[29]が得られている．夜間頻尿の発症は，サーカディアンリズムを含めての生活習慣全般が関連している可能性が高く，適切な生活指導法の開発についても今後考慮する必要がある．

睡眠障害の治療の多くは，単に睡眠薬を投与することが多いが，泌尿器疾患が起因となっている睡眠障害，むずむず脚症候群のような特異な睡眠障害には効果のない場合が多い．これらが睡眠障害患者への睡眠薬の多剤投与や，常用量以上の多量の薬剤投与につながっている可能性は否定できない．高齢者の30％近くが，何らかの睡眠障害を発症している可能性が指摘されている現在，高齢者の睡眠障害治療において，エビデンスに基づく医療を提供することが望ましい．このような面からも，早急に高齢者の夜間頻尿の原因分類と治療指針の確立が期待される．

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Exp Brain Res (2005) 166: 263–276
DOI 10.1007/s00221-005-2358-y

RESEARCH ARTICLE

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Functional significance of delay-period activity of primate prefrontal neurons in relation to spatial working memory and reward/omission-of-reward expectancy

Received: 9 September 2004 / Accepted: 17 March 2005 / Published online: 21 July 2005

Abstract The lateral prefrontal cortex (LPFC) is important in cognitive control. During the delay period of a working memory (WM) task, primate LPFC neurons show sustained activity that is related to retaining task-relevant cognitive information in WM. However, it has not yet been determined whether LPFC delay neurons are concerned exclusively with the cognitive control of WM task performance. Recent studies have indicated that LPFC neurons also show reward and/or omission-of-reward expectancy-related delay activity, while the functional relationship between WM-related and reward/omission-of-reward expectancy-related delay activity remains unclear. To clarify the functional significance of LPFC delay-period activity for WM task performance, and particularly the functional relationship between these two types of activity, we examined individual delay neurons in the primate LPFC during spatial WM (delayed response) and non-WM (reward–no-reward delayed reaction) tasks. We found significant interactions between these two types of delay activity. The majority of the reward expectancy-related neurons and the minority of the omission-of-reward expectancy-related neurons were involved in spatial WM processes. Spatial WM-related neurons were more likely to be involved in reward expectancy than in omission-of-reward expectancy. In addition, LPFC delay neurons observed during the delayed response task were not concerned exclusively with the cognitive control of task performance; some were related to reward/omission-of-reward expectancy but not to WM, and many showed more memory-related activity for preferred rewards than for less-desirable rewards. Since employing a more preferred reward induced better task performance in the monkeys, as well as enhanced WM-related neuronal activity in the LPFC, the principal function of the LPFC appears to be the integration of cognitive and motivational operations in guiding the organism to obtain a reward more effectively.

Keywords Delayed response · Monkey · Prefrontal cortex · Reward · Working memory

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Introduction

The lateral prefrontal cortex (LPFC) is thought to play its most important role in cognitive control (Fuster 1997; Miller and Cohen 2001), particularly in retaining and manipulating information in working memory (WM) (Goldman-Rakic 1996). LPFC-injured patients and monkeys with LPFC ablation show severe deficits in the learning and performance of WM tasks, including delayed response, delayed alternation and delayed matching to sample tasks (Jacobsen 1935; Mishkin 1957; Passingham 1975; Freedman and Oscar-Berman 1986). Human neuroimaging studies have demonstrated activation of the LPFC in association with WM task performance (D'Esposito et al. 1998; Owen et al. 1998). During the delay period of a WM task, primate LPFC neurons show sustained activity (Kubota and Niki 1971; Fuster 1973; Niki 1974; Kojima and Goldman-Rakic 1982; Quintana et al. 1988) and many show differential delay activity depending on differences in the spatial or object cues (Niki 1974; Quintana et al. 1988; Funahashi et al. 1989). Delay neurons with cue-related differential activity are thought to be involved in retaining task-relevant cognitive

information in WM, although the functional significance of delay neurons without cue-related differential activity remains unclear. Furthermore, it has not yet been determined whether delay neurons observed during WM tasks are concerned exclusively with the cognitive control of task performance.

Recently, delay-period activity that is not associated with WM has been reported in the monkey LPFC, particularly in LPFC delay neurons that are related to motivational operations, namely reward expectancy (Watanabe 1996; Leon and Shadlen 1999; Roesch and Olson 2003) and omission-of-reward expectancy (that is, anticipation of no-reward as the trial outcome during the reward–no-reward delayed reaction task) (Watanabe et al. 2002). These neurons show a differential delay activity between reward and no-reward trials, and/or among trials in which different types of reward might or might not be expected.

We reported previously that LPFC delay neurons showed both spatial WM-related and reward expectancy-related activities during a delayed response task using several different types of reward (Watanabe 1996). In an oculomotor delayed response task with both reward-present and reward-absent conditions, Kobayashi et al. (2002) reported both spatial WM-related and reward/omission-of-reward expectancy-related LPFC neurons. However, the functional relationship between the reward/omission-of-reward expectancy-related and spatial WM-related neuronal activities remains unclear. In order to clarify the functional significance of delay-period activity for WM task performance, and particularly the functional relationship between these two types of delay-period activity, we examined individual LPFC delay neurons during both WM and non-WM tasks; that is, spatial-memory (spatial delayed response) and outcome-expectancy (reward–no-reward delayed reaction) tasks. In addition, we examined whether neurons that showed delay (either differential or non-differential) activity in one type of task also showed delay (particularly differential delay) activity in the other. Furthermore, we examined individual LPFC delay neurons during both types of task in relation to their spatial and reward discrimination.

We postulated that not all delay neurons observed during the spatial-memory task would be concerned with the cognitive control of WM task performance, as delay-period activity was also observed during a non-WM task in the monkey LPFC (Watanabe et al. 2002). We further suggested that there would be some associations between WM-related and reward/omission-of-reward expectancy-related activities, as monkeys perform the WM task to obtain a reward and are reluctant to perform the task when no reward is expected. We made the following specific predictions: first, that more reward-expectancy than omission-of-reward expectancy neurons would show delay-period activity and would be concerned with retaining spatial information in WM during the spatial-memory task; second, that the majority of omission-of-reward expectancy neurons would not be involved in retaining information in WM; and third, that WM-related neurons would be more concerned with reward expectancy than with omission-of-reward expectancy.

We found that the majority of reward-expectancy neurons and the minority of omission-of-reward expectancy neurons were involved in spatial WM processes. We also discovered that spatial WM neurons were more likely to be involved in reward expectancy than in omission-of-reward expectancy. In addition, the data indicated that not all delay neurons observed during the spatial-memory task were concerned directly with the cognitive control of WM task performance.

Materials and methods

Subjects and behavioral training

Three male Japanese monkeys (*Macaca fuscata*) weighing 5.5–6.5 kg were used in this study. The monkeys were trained on an outcome-expectancy (reward–no-reward delayed reaction) task and a spatial-memory (spatial delayed response) task. Each monkey faced a panel that was positioned 33 cm away at eye level. The panel displayed three horizontally arranged rectangular windows (6×7.5 cm), three horizontally arranged circular keys (diameter = 5 cm) and a holding lever (width = 5 cm, protrusion = 5 cm) (Fig. 1a). The distance between adjacent rectangular windows, and between adjacent circular keys, was 10 cm from center to center. The distance between each rectangular window and the circular key immediately below it was 8 cm from center to center. Each window contained one opaque screen and one transparent screen with thin vertical lines. In the outcome-expectancy task, only the center window, center key and holding lever were used. In the spatial-memory task, the two windows on the left and right, the two keys on the left and right, and the holding lever were used.

outcome-expectancy task

There were three versions of this task: visible food, cued food and cued liquid. In the visible-food version (Fig. 1b), the monkey initially depressed the lever for 10–12 s (Pre-inst). The opaque screen of the window was then raised to reveal a food tray, either with (reward trial) or without (no-reward trial) a reward behind a transparent screen, for a 1-s duration as an instruction (Inst). After a delay of 5 s (Delay), a white light appeared on the key as a go signal (Go signal). When the monkey released the hold lever and pressed the key within 2 s after the go signal, both screens were raised and the monkey either collected the food reward (reward trials) or went unrewarded (no-reward trials), depending on the trial type. Reward and no-reward trials were alternated pseudo-randomly at a ratio of 3:2. Even in no-reward trials, the monkey had to press the key in order to advance to the next trial. In other versions of the outcome-expectancy task, a 1-s long color instruc-

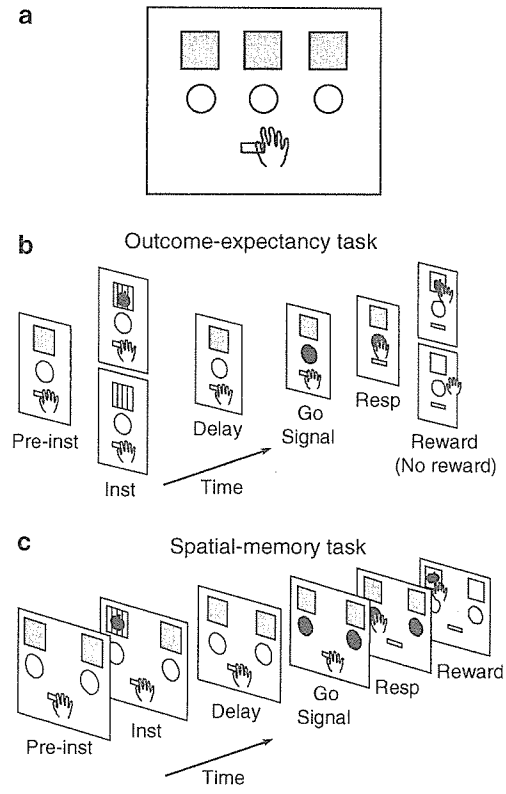

Fig. 1 The experimental panel and sequence of events used in the two types of task. **a** The experimental panel contained three horizontally arranged windows, three horizontally arranged keys and a holding lever. **b** The sequence of events in the visible-food version of the outcome-expectancy task. For brevity, only the center window, center key and holding lever are illustrated. The *upper panel* represents the reward trials and the *lower panel* represents the no-reward trials. *Inst* Instruction, *Resp* Response. **c** The sequence of events in the visible-food version of the spatial-memory task. For brevity, only the two (*left* and *right*) windows, two keys and holding lever are illustrated

tion (red or green) on the key indicated whether a reward would be delivered: red indicated reward trials and green indicated no-reward trials. In the cued-food version, depending on the instruction, a food reward could be collected (reward trials) or not collected (no-reward trials) behind the screens at the end of the trial. In the cued-liquid version, a drop of liquid was delivered (reward trials) or not delivered (no-reward trials) through a tube positioned close to the mouth of the monkey. Pieces (about 0.5 g) of raisin, sweet potato, cabbage or apple were used as food rewards. Drops (0.3 ml) of water, sweet isotonic beverage, orange juice or grape juice were used as liquid rewards. The same reward was used continuously for a block of about 50 trials; it was assumed that the animal knew, which reward was being used in each block after two or three trials. Each instruction stimulus was thus associated with the presence or absence of a particular kind of reward. The monkeys were not required to perform any differential operant action related to differences between the rewards. In the food-reward tasks, both windows were closed when the monkey returned its hand to the holding lever after the key press. The trial was aborted if the monkey released the hold lever before the go signal.

spatial-memory task

There were three versions of this task: visible food, cued food and cued liquid. In the visible-food version (Fig. 1c), the monkey initially depressed the lever for 10–12 s (Pre-inst). The opaque screen of the left or right window was then raised to reveal a food tray behind a transparent screen for a 1-s duration as an instruction (Inst). After a delay of 5 s (Delay), a white light appeared on the left and right keys as a go signal (Go signal). When the monkey released the hold lever and correctly pressed the key on the indicated side within 2 s after the go signal, the left and right screens were raised and the monkey could collect the food reward. When the monkey did not respond to the correct side, the trial ended without the window opening. In the cued-food and cued-liquid versions of the spatial-memory task, a red light was presented on the left or right key for a 1-s duration to indicate the correct side for the response. After a delay of 5 s, a go signal of white light appeared on both keys, and the monkey was required to touch the key on the cued side within 2 s after the go signal. Correct responses were rewarded with the food or liquid. The rewards and methods of reward delivery used during the spatial-memory task were the same as those used in the outcome-expectancy task. The same reward was used continuously for a block of about 50 trials.

The task was controlled using a personal computer (NEC, PC9801FA, Tokyo). No attempt was made to restrict the eye movements of the animals. On weekdays, the monkeys received their daily liquid requirement while performing the task. Water was available ad libitum during weekends. Monkey pellets were available ad libitum in the home cage at all times, while more preferred foods were used as rewards in the laboratory experiments.

Reward-preference tests

The reward preferences of each monkey were assessed in separate blocks of choice trials before or after the behavioral testing of each animal. Preferences for different foods were assessed in free-choice tests by simultaneously presenting several items to the monkey. Preferences for different reward liquids were assessed by testing the willingness of each monkey to perform the task with one liquid after it had refused to perform the task with another.

Surgery and recording

Details of the procedure are described elsewhere (Watanabe et al. 2002). Briefly, on completion of training, each monkey was surgically prepared under sodium pentobarbital anesthesia (Nembutal; 30 mg/kg).