Ⅲ. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kuriyama K, Mishima K, Suzuki H, Aritake S, Uchiyama M	Sleep accelerates the improvement in working memory performance.	J Neurosci	28	10145-10150	2008
Aritake S, Uchiyama M, Suzuki H, Tagaya H, Kuriyama K, Matsuura M, Takahashi K, Higuchi S, Mishima K	Time estimation during stable sleep dependent on progression on sleep.	Neurosci Res	in press		
Yokoyama E, Saito Y, Kaneita Y, Ohida T, Harano S, Tamaki T, Ibuka E, Kaneko A, Nakajima H, Takeda F	Association between subjective well-being and sleep among the elderly in Japan.	Sleep Medicine	9	157-164	2008
Kaneita Y, Yokoyama E, Harano S, Tamaki T, Suzuki H,Munezawa T, Nakajima H, Asai T, Ohida T	Associations Between Sleep Disturbance and Mental Health Status: A Longitudinal Study of Japanese Junior High School Students.	Sleep Medicine	In press		
Nomura T, Inoue Y, Kusumi M, Oka Y, Nakashima K.	Email-based epidemiological surveys on restless legs syndrome in Japan.	Sleep and Biological Rhythms	6(3)	139-145	2008
Endo Y, Suzuki M, Sato M, Namba K, Hasegawa M, Matsuura M, Inoue Y	Prevalence of Complex Sleep Apnea Among Japanese Patients with Sleep Apnea Syndrome.	Tohoku J. Exp. Med.	215 (4)	349-354	2008
Hazama G, Inoue Y, Kojima K, Ueta T, Nakagome K	The Prevalence of Probable Delayed Sleep Phase Syndrome in Students from Junior High School to University in Tottori	Tohoku J. Exp. Med.	216 (1)	95-98	2008
Oka Y, Suzuki S, Inoue Y	Bedtime Activities, Sleep Environment, and Sleep/Wake Patterns of Japanese Elementary School Children.	Behav Sleep Med.	6(4)	220-233	2008
Komada Y, Inoue Y, Hayashida K, Nakajima T, Honda M, Takahashi K	Clinical significance and correlates of behaviorally induced insufficient sleep syndrome.	Sleep Med.	9(8) :	851-856	2008
Nomura T, Inoue Y, Kusumi M, Uemura Y, Nakashima K	Prevalence of restless legs syndrome in a rural community in Japan.	Mov Disord.	23(16)	2363-2369	2008

Ozaki A, Inoue Y, Nakajima T, Hayashida K, Honda M, Komada Y, Takahashi K	Health-related quality of life among drug-naïve patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time.	J Clin Sleep Med.	4(6)	572-578	2008

Ⅳ. 研究成果の刊行物・別刷

Behavioral/Systems/Cognitive

Sleep Accelerates the Improvement in Working Memory Performance

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Working memory (WM) performance, which is an important factor for determining problem-solving and reasoning ability, has been firmly believed to be constant. However, recent findings have demonstrated that WM performance has the potential to be improved by repetitive training. Although various skills are reported to be improved by sleep, the beneficial effect of sleep on WM performance has not been clarified. Here, we show that improvement in WM performance is facilitated by posttraining naturalistic sleep. A spatial variant of the *n*-back WM task was performed by 29 healthy young adults who were assigned randomly to three different experimental groups that had different time schedules of repetitive *n*-back WM task sessions, with or without intervening sleep. Intergroup and intersession comparisons of WM performance (accuracy and response time) profiles showed that *n*-back accuracy after posttraining sleep was significantly improved compared with that after the same period of wakefulness, independent of sleep timing, subject's vigilance level, or circadian influences. On the other hand, response time was not influenced by sleep or repetitive training schedules. The present study indicates that improvement in *n*-back accuracy, which could reflect WM capacity, essentially benefits from posttraining sleep.

Key words: sleep; working memory capacity; memory consolidation; *n*-back task; skill learning; intelligence

Introduction

Working memory (WM) is understood to be a cognitive system for both the temporary storage and manipulation of remembered information. It is regarded as a specific process by which a remembered stimulus is held "on-line" to guide behavior in the absence of external cues or prompts (Baddeley and Hitch, 1974; Goldman-Rakic, 1996; Owen et al., 1996). The maximum amount of information that can be retained in the WM, referred to as WM capacity, is an important factor for determining problem-solving and reasoning ability (Kyllonen and Christal, 1990; Fry and Hale, 1996; Hale et al., 1997). The WM encompasses the concept of traditional "short-term memory," and consequently both WM and short-term memory share cognitive architecture and functional neuroanatomy. Miller (1956) reported that the capacity for WM (which is still sometimes called "short-term" memory) in healthy adults is restricted to within $\sim 7 \pm 2$ chunks. Since then, it has been firmly believed that there exists a limit to the capacity of WM, and subsequent studies confirmed that this limit is approximately 4 items without the use of any hidden strategies (Luck and Vogel, 1997; Cowan, 2001).

The "*n*-back" procedure (Gevins and Cutillo, 1993; Callicott et al., 1998, 1999; McEvoy et al., 1998) has been used in many human studies to investigate the characteristics of WM performance or the neural basis of WM processes (Callicott et al., 1998; Jansma et al., 2004; Mattay et al., 2006). A very recent study has shown that the limit to WM capacity is determined by the ability to remember only relevant information, and that the prefrontal cortex and basal ganglia activities preceding the filtering of irrelevant information are associated with interindividual differences in WM capacity (McNab and Klingberg, 2008). Some studies have shown that the training of WM may lead to effects that go beyond a specific training effect (Olesen et al., 2004; Westerberg and Klingberg, 2007; Jaeggi et al., 2008). Olesen et al. (2004) presented progressive evidence obtained by functional magnetic resonance imaging that repetitive training improves spatial WM performance [both accuracy and response time (RT)] associated with increased cortical activity in the middle frontal gyrus and the superior and inferior parietal cortices. Such a finding suggests that training-induced improvement in WM performance could be based on neural plasticity, similar to that for other skill-learning characteristics.

A growing body of literature in recent years holds that sleep plays a crucial role in the development of skill learning. Evidence of sleep-dependent skill learning has now been demonstrated across a wide variety of skill domains, including the visual (Karni et al., 1994; Gais et al., 2000; Stickgold et al., 2000), auditory (Atienza et al., 2004; Gaab et al., 2004), and motor (Smith and MacNeill, 1994; Fischer et al., 2002; Walker et al., 2002, 2003; Kuriyama et al., 2004) systems. Specifically, sleep has been implicated in the ongoing process of consolidation after initial acquisition, whereby delayed learning could occur in the absence of further practice (Smith, 1995; Stickgold et al., 2001; Walker and Stickgold, 2004).

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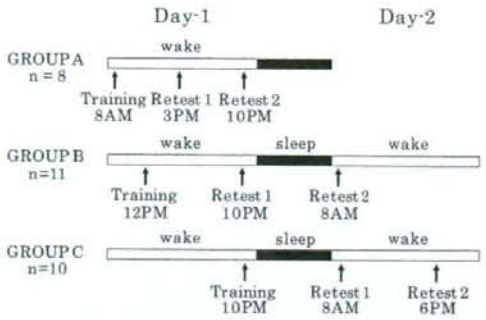

Figure 1. Study protocol. Twenty-nine subjects were allocated into three experimental groups (A–C). Group A was trained at 8:00 A.M. and retested at 3:00 P.M. and 10:00 P.M. across wakefulness. Group B was trained at 12:00 P.M. (midday) and retested at 10:00 P.M. (after 10 h of wakefulness) and at 8:00 A.M. (10 h later) after a night of sleep. Group C was trained at 10:00 P.M. and retested at 8:00 A.M. (10 h later) after a night of sleep and at 6:00 P.M. (after 10 h of wakefulness).

We hypothesized that improvement in WM performance as measured by the *n*-back procedure could be facilitated by posttraining physiological sleep similar to that observed in other skill domains. In this study, we made a particular attempt to discriminate the possible effects of time elapsed after training, posttraining brain state (sleep or wakefulness), and circadian fluctuations in the improvement of *n*-back task performance.

Materials and Methods

Participants

A total of 29 right-handed healthy subjects (mean age, 21.9 years; range, 19–26 years; 19 females) were randomly assigned to three different groups (described below). Subjects had no previous history of drug or alcohol abuse or of neurological, psychiatric, or sleep disorders, and were maintaining a constant sleep schedule. They were instructed to be drug-, alcohol-, and caffeine-free for 24 h before, and during, the study period. All procedures for the study were in accordance with the guidelines outlined in the Declaration of Helsinki. The study protocol was approved by the Intramural Research Board of the National Center of Neurology and Psychiatry, and all subjects provided written informed consent to participate in the study.

Working memory task

We used a spatial variant of the *n*-back WM task, which has been widely used to measure spatial WM with a sustained attention component (Gevins and Cutillo, 1993; Callicott et al., 1998, 1999; McEvoy et al., 1998), for all three experimental groups (groups A–C) (for details, see Fig. 1 and below). Subjects performed the *n*-back WM task with nine increasing levels of difficulty (n = 1–9), using a standard PC. Four large dots presented in a single row were displayed on the screen, indicating the four possible places where a stimulus could appear (Fig. 2). The stimulus consisted of one dot changing color. Subjects were instructed to respond by pushing one of four buttons on a response button box with the right fingers as quickly and as accurately as possible when the next stimulus appeared. The layout of the four buttons corresponded spatially to the four possible positions in which the stimulus appeared. Responses were to be made after a delay of n (load level) in *n*-back stimuli. The load level was shown before stimulation began throughout the entire experimental task. The different load levels were run in blocks of 20 + n stimuli; thus, 20 responses were obtained at each load level. The interstimulus interval was set at 500 ms, and each stimulus was displayed for 1500 ms; each block lasted a total of 41,500–58,500 ms. At each level, subjects performed three trials separated by 15,000 ms rest periods, with the scores being averaged at the end of the three trials. The stimuli were set in randomized order for each test session. Subjects completed all load levels (n = 1–9) three times in each test session (see below, Experimental design).

Performance measures

Performance was evaluated by using both the average percentage of correct responses (accuracy) and the average RT at each different load level. These provided measures of improvement in the throughput and the processing speed of the WM, respectively. The detection threshold for a given session was defined as the maximum *n*-back accuracy level (NL) at which the subject's accuracy exceeded at least 80%. RT was also calculated for each session.

Experimental design

The 29 subjects were assigned to the three experimental groups listed below, and each group underwent a specific schedule consisting of an initial training session and two retest sessions. Subjects performed a spatial *n*-back WM task (n = 1–9) in each test session. All morning retests were performed at least 1 h after awakening. Just before the initial training session, each subject performed the spatial *n*-back task (n = 0–4) to become familiar with the PC procedure. Retest schedules (Fig. 1) were as follows.

Group A: continued WM task training across wakefulness. To determine whether the simple passage of time (across wakefulness) led to improvement in WM performance, eight subjects (mean age, 22.3 years; range, 19–26 years; 5 females) were retested at 7 h intervals across the day after initial training at 8:00 A.M. (i.e., retests at 3:00 P.M. and 10:00 P.M.)

Group B: continued WM task training followed by 10 h wakefulness and then sleep. To determine whether subsequent sleep showed any marked improvement in WM performance over wakefulness, 11 subjects (mean age, 21.4 years; range, 19–24 years; 7 females) were trained at 12:00 P.M. (midday) and retested once at 10:00 P.M. after 10 h of wakefulness, and then again at 8:00 A.M. the next morning after a night of sleep.

Group C: continued WM task training followed by the immediate 8 h sleep and then wakefulness. To determine whether the improvement of WM performance required sustained wakefulness just after the initial training, 10 subjects (mean age, 20.2 years; range, 19–22 years; 7 females) were trained at 10:00 P.M. followed by an immediate 8 h sleep and then retested at 8:00 A.M. the next morning, and again later at 6:00 P.M. on the same day.

At each training and retesting point, all subjects performed a simple reaction task, which provided their simple reaction time (SRT), a standard measure of subjective alertness (Lorenzo et al., 1995; Corsi-Cabrera et al., 1996). The amount of overnight sleep for each subject in each experimental group was estimated using a self-recorded sleep log.

Statistics

Two-way factorial ANOVA was applied to detect the group and test-session differences in SRT performance. One-way factorial ANOVA was applied to compare the amount of sleep in the previous night of the experiment among three groups. The χ^2 test was used to compare gender distribution of the study subjects among the three groups.

Two-way factorial ANOVA was applied to detect the load level and gender differences in baseline *n*-back task performance in the three experimental groups (A–C), as well as to compare the improvement of *n*-back task performance among the three groups by 3 (experimental groups) × 3 (test sessions) and by 3 (experimental groups) × 2 (inter-sessions; retest 1 minus initial training vs retest 2 minus retest 1) comparison. After the analyses, we used one-way factorial ANOVA to detect the possible role of posttraining sleep in the improvement of *n*-back task performance. All ANOVA were followed by Bonferroni's *post hoc* test. Results are shown as mean and SEM values. A p value of <0.05 (<0.0167 in Bonferroni's *post hoc* analysis) was considered to indicate significance.

Results

Sleep quality and alertness

Two-way ANOVA revealed no significant differences in SRT within the three experimental groups ($F_{(2,78)} = 1.920$; $p = 0.1535$; 507.5 ± 18.0 vs 468.7 ± 12.3 vs 486.1 ± 10.4 ms for groups A–C, respectively) or within the three test sessions ($F_{(2,78)} = 0.076$; $p =$

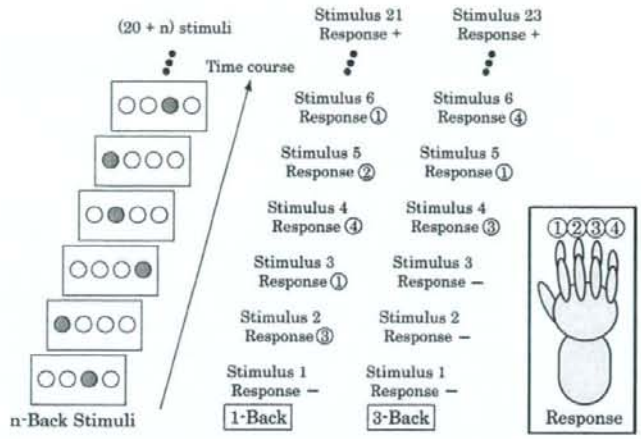

Figure 2. The spatial variant of the *n*-back working memory task configurations. Four large white dots aligned in a single row were displayed on the screen, indicating the four possible places where a stimulus could appear. The stimulus consisted of one of the four dots changing from white to red. Subjects had to respond to the stimulus by pushing one of four buttons, which were arranged in lines corresponding spatially to the four possible stimulus positions, with the right fingers as quickly and accurately as possible when the next stimulus appeared. Responses had to be made after a delay of *n* (*n*-back) stimuli. The different load levels (1–9) were run in blocks of 20 + *n* stimuli; thus, 20 responses were obtained at each load level. The interstimulus interval was set at 500 ms, and a stimulus was displayed for 1500 ms. Arrangement of the stimuli was randomized in each test session.

0.9267; 488.6 ± 17.2 vs 482.5 ± 11.5 vs 485.1 ± 11.4 ms for initial training, retest 1, and retest 2, respectively). In addition, no interaction in SRT between the experimental groups and test sessions ($F_{(4,78)} = 0.250$; $p = 0.9090$) was found. One-way ANOVA detected no significant difference in the amount of sleep among the experimental groups ($F_{(2,26)} = 2.872$; $p = 0.0747$; 7.31 ± 0.19 vs 7.55 ± 0.22 vs 6.85 ± 0.22 h for groups A–C, respectively). These findings indicate that there were no clear differences in vigilance level among the subjects in each test session.

Initial training analyses

We analyzed the difficulty profiles of accuracy and RT for each load level in the *n*-back task for each experimental group (A–C). Two-way ANOVA revealed significant differences in accuracy among load levels ($F_{(8,294)} = 114.1$; $p < 0.001$) (Fig. 3), but not among experimental groups ($F_{(2,294)} = 2.905$; $p = 0.0567$). No interaction was seen between load levels and experimental groups ($F_{(16,294)} = 0.954$; $p = 0.5086$) in terms of accuracy. A *post hoc* test for the load level revealed a significant decrement in accuracy between load level 5 and load level 6 ($p < 0.0001$), in that task difficulty gradually increased with an increase in trial number (n) up to 5; it then sharply increased at trial 6 and thereafter remained high.

Two-way ANOVA revealed no significant differences in RT either among load levels ($F_{(8,294)} = 0.304$; $p = 0.9641$) (Fig. 3) or among experimental groups ($F_{(2,294)} = 2.520$; $p = 0.0826$). No interaction was seen between load levels and experimental groups ($F_{(16,294)} = 0.122$; $p > 0.9999$) in terms of RT.

Gender effects on WM performance have been speculated in a previous study (Duff and Hampson, 2001). We therefore examined gender distribution in each experimental group. The χ^2 test revealed no significant gender distribution among the experimental groups ($\chi^2 = 0.138$; $p = 0.9331$), suggesting that each group included almost equal gender distribution. Two-way ANOVA revealed no significant gender difference in accuracy (male vs female; 68.34 ± 2.39% vs 67.18 ± 1.84%; $F_{(1,243)} = 0.696$; $p = 0.4048$), but there were significant load level differences in accuracy ($F_{(8,243)} = 108.3$; $p < 0.001$) on the WM task, although no significant interaction was observed between gender and load level in terms of accuracy ($F_{(8,243)} = 0.908$; $p = 0.5106$). Likewise, two-way ANOVA revealed no significant gender difference in RT (male vs female; 299.5 ± 13.4 ms vs 325.7 ± 13.0 ms; $F_{(1,243)} = 1.580$; $p = 0.2100$) and no significant load level difference ($F_{(8,243)} = 0.245$; $p = 0.9817$) in RT. Moreover, no significant interaction was seen between gender and load level in terms of RT ($F_{(8,243)} = 0.294$; $p = 0.9842$). These findings indicate that there was no gender difference in initial training performance.

Analyses for experimental group × test-session interaction

Two-way ANOVA (3 experimental groups × 3 test sessions) showed significant group and test-session effects on NL ($F_{(2,78)} = 4.147$, $p = 0.0194$; $F_{(2,78)} = 7.019$, $p = 0.0016$; respectively) (Fig. 4), but no significant group × test-session interaction ($F_{(4,78)} = 1.453$; $p = 0.2246$). Two-way ANOVA (3 groups × 2 intersessions) showed significant group effects on NL improvement ($F_{(2,52)} = 3.686$; $p = 0.0318$) and a significant group × intersession interaction ($F_{(2,52)} = 15.857$; $p < 0.0001$) (Fig. 5), but no significant intersession effect on NL improvement ($F_{(1,52)} = 0.248$; $p = 0.6205$). A *post hoc* test for NL improvement revealed a significant difference between groups A and C ($p = 0.0109$), and a trend toward intergroup differences between groups A and B ($p = 0.0491$). These findings suggest that the three experimental groups showed different time profiles of NL improvement; NL improvement during posttraining sleep was significantly greater than that during wakefulness, and the acquired NL improvement seemed to be maintained for at least 10 h after posttraining sleep. As a result, average NL improvement in subjects who experienced posttraining sleep (groups B and C) was greater than that in subjects who went through the same period of wakefulness (group A) (Fig. 5).

Two-way ANOVA (3 experimental groups × 3 test sessions) showed neither significant group nor test-session effects on RT ($F_{(2,78)} = 0.719$, $p = 0.4904$; $F_{(2,78)} = 0.027$, $p = 0.9738$; respectively) (Fig. 4); moreover, no significant group × test-session interaction was observed ($F_{(4,78)} = 0.307$; $p = 0.8723$).

Group A: continued WM task training across wakefulness

One-way ANOVA revealed no significant test-session difference in NL in group A subjects ($F_{(2,21)} = 0.218$; $p = 0.8058$). Compared with the NL for the initial training (3.13 ± 0.72), we observed a subtle but not statistically significant improvement in NL at 3:00 P.M. (3.63 ± 0.71, by 16.0% vs initial training) and at 10:00 P.M. (3.75 ± 0.70, by 19.8% vs initial training) (Fig. 4*A*), suggesting that the simple passage of time across wakefulness produced no significant improvement in WM performance beyond that expected on the basis of continued rehearsal.

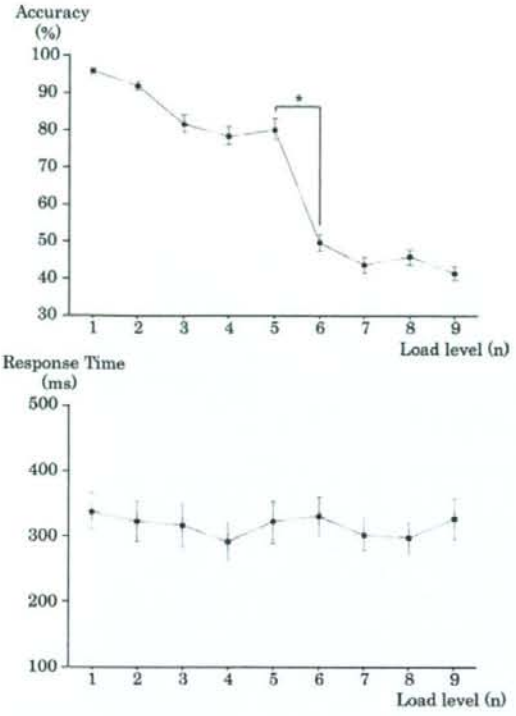

Figure 3. Initial training performances in all groups. Accuracy (top) and RT (bottom) in the initial training session for each load level are plotted. Filled circles with error bars represent mean and SEM values in each panel. Significant interload level difference in accuracy was observed between level 5 and level 6; the accuracy linearly decreased as the task difficulty increased up to level 5 before rapidly dropping at level 6 and remaining low at <50% thereafter. We observed no significant interload level difference in RT. *$p < 0.0001$.

Group B: continued WM task training after wakefulness and then sleep

One-way ANOVA revealed significant test-session differences in NL in group B subjects ($F_{(2,30)} = 5.104$; $p = 0.0124$). A *post hoc* test for NL revealed significant differences between the following test sessions: initial training versus retest 2 (4.00 ± 0.40 vs 5.73 ± 0.49; $p = 0.0081$) and retest 1 versus retest 2 (4.09 ± 0.39 vs 5.73 ± 0.49; $p = 0.0116$).

Similarly to group A subjects, group B subjects demonstrated no significant increase in NL at 10:00 P.M. (by 2.25% vs initial training; $p = 0.8822$) (Fig. 4*B*), but demonstrated a significant increase in NL at retest 2 the next morning (by 40.1% vs retest 1 before sleep). These data suggest that the significant improvement in NL was obtained not during the 10 h of wakefulness just after initial training but after the posttraining sleep 10 h or more after the initial training.

Group C: continued WM task training after sleep and then wakefulness

One-way ANOVA revealed significant test-session differences in NL in group C subjects ($F_{(2,27)} = 14.678$; $p < 0.0001$). A *post hoc* test for NL revealed significant differences between the following test sessions: initial training versus retest 1 (3.30 ± 0.35 vs 4.90 ± 0.20; $p = 0.0002$) and initial training versus retest 2 (3.30 ± 0.35 vs 5.10 ± 0.28; $p < 0.0001$).

After a night of posttraining sleep, a significant increase in NL was apparent at 8:00 A.M. the next morning compared with the initial training scores (by 48.5%) (Fig. 4*C*). However, an additional 10 h of wakefulness produced no significant change in NL compared with the retest 1 scores (by 4.08%; $p = 0.4577$).

Discussion

Sleep-dependent facilitation of WM performance improvement

Although the NLs at the initial training session were comparable among all experimental groups or by gender, subjects demonstrated remarkably different time courses of subsequent NL improvements that were specifically dependent on the timing of posttraining sleep. Subjects trained at 12:00 P.M. (midday) demonstrated no significant improvement when retested after 10 h of wakefulness, but showed a significant improvement at 8:00 A.M. after a night of posttraining sleep (by 40.1% in group B) (Fig. 4). Similarly, subjects trained at 10:00 P.M. showed a significant overnight improvement (by 48.5% in group C) (Fig. 4), but no significant additional improvement during a further 10 h of wakefulness. Thus, significant improvements were acquired only across a night of posttraining sleep and not over a similar period of wakefulness, regardless of whether the time awake or time asleep came first.

The possibility that circadian factors confounded the learning profiles after 10 h of wakefulness is unlikely. The initial training session was similar for subjects trained at 8:00 A.M., 12:00 P.M., or 10:00 P.M., as was the case for objective ratings of alertness across all testing points. Thus, we consider sleep itself to be the most likely source of the improvement in NL on the *n*-back task.

RT has been considered to be a good indicator of skill performance improvement (Fischer et al., 2002; Walker et al., 2002; Kuriyama et al., 2004), but in the present study, it rarely seemed to reflect improvement in WM task performance. In our subjects, RT values varied independently of the comparative difficulty of the *n*-back task, which is in contrast to the values observed in the accuracy profiles for initial training. A previous study involving repetitive WM task training has also shown marked improvement in accuracy values over a 1–2 d period, although RT values improved slowly over a 4–5 d period (Olesen et al., 2004). Taking together, these findings suggest that RT may reflect different levels of improvement in WM task performance on the basis of accuracy values. WM performance is considered to be a result of plural cognitive processing (Gevins and Cutillo, 1993; Owen et al., 1996). The RT value possibly reflects the total skill performance of WM, whereas accuracy reflects the capacity limitation of WM.

Possible contribution of improvement in *n*-back accuracy to generalized improvement of WM performance

The results of recent investigations using a spatial variant of the WM task to examine the feasible number of items for both storing temporary and manipulating data converged on around three or four items (Luck and Vogel, 1997; Cowan, 2001; Saults and Cowan, 2007). The accuracy index for the *n*-back task has been established as a refection of WM capacity in previous studies, and has been used for investigating individual or age variation in WM capacity (Oberauer, 2005; Mattay et al., 2006). Consistent with these previous findings, our subjects in all experimental groups showed NL around 3 or 4 at the initial training session. In the postsleep session, the NL for groups B and C increased up to around 5 and 6. Thus, the NL improvement was acquired across sleep, suggesting that dynamic changes in the WM process were executed during sleep, as has been observed in other cases of skill

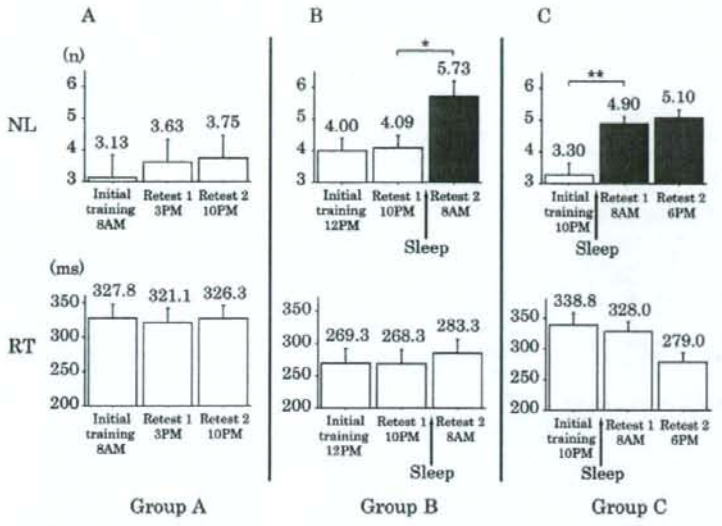

Figure 4. Time courses of improvement in *n*-back task performance. Time courses of NL (top) and RT (bottom) are displayed. ***A–C***, Bars and error bars represent mean and SEM values in groups A–C, respectively. In the sessions after posttraining sleep, we observed significant improvement in NL compared with those before sleep (groups B and C; black bars), but RT showed no significant benefit from sleep. $*p < 0.0167$; $**p < 0.001$.

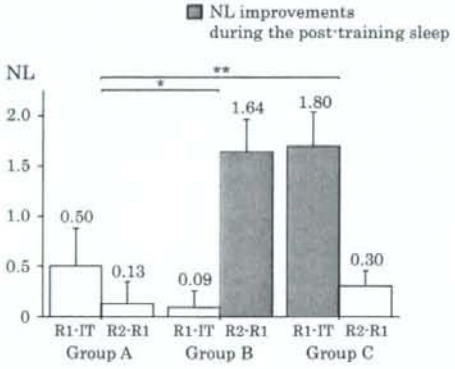

Figure 5. Intersession differences in improvement in *n*-back accuracy. Bars and error bars represent mean and SEM values of intersession differences in NL in each group. Left and right bars in each experimental group show intersession differences in NL between initial training (IT) and retest 1 (R1) sessions, and between R1 and R2 sessions, respectively. Filled bars represent NL improvements during the posttraining sleep in groups B and C. *Post hoc* test revealed a significant intergroup difference in NL between groups A and C ($**p = 0.0109$) and a trend toward intergroup difference in NL between groups A and B ($*p = 0.0491$).

learning (Stickgold et al., 2000; Walker et al., 2002; Kuriyama et al., 2004).

Some studies focusing on sleep-dependent skill learning have emphasized that the sleep-dependent gains seen in procedural skills were specific to the stimulus materials used, which therefore could not affect skill performance using other stimuli (Korman et al., 2003; Walker et al., 2003). Thus, the sleep-dependent benefit on the *n*-back task observed in the present study might be limited to the particular stimulus we used and may not be generalizable to other WM tasks.

However, Jaeggi et al. (2008) have recently demonstrated the landmark finding that repetitive training on a spatial *n*-back task improved not only spatial *n*-back performance but also auditory *n*-back performance simultaneously. Moreover, they found that the performance improvement on the *n*-back task could involve the improvement of general fluid intelligence as measured by a standardized fluid intelligence test (Jaeggi et al., 2008). Olesen et al. (2004) reported training-induced changes in cortical activity after 5 weeks of WM training, and the increment of WM load showed increased cortical activity in the middle frontal gyrus and superior and inferior parietal cortices, where activity changes are known to be less specific to various stimuli that drive cognitive performance (Klingberg, 1998; Duncan and Owen, 2000).

Together, these findings suggest that improvement in WM performance might not depend on the type of stimulus used, and that the sleep-dependent improvement in WM performance seen in the present study may lead to various improvements in WM performance, and furthermore, in the general capacity of WM. WM capacity is an important factor in a wide range of cognitive abilities, including general fluid intelligence (Conway et al., 2003; Colom et al., 2007), and our finding together with that of Jaeggi et al. (2008) suggests that posttraining sleep with appropriate timing could be a potent facilitating factor in WM training, leading to the advancement of individual general fluid intelligence.

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Time estimation during sleep relates to the amount of slow wave sleep in humans

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ABSTRACT

Humans have the ability to estimate the amount of time that has elapsed during sleep (time estimation ability; TEA) that enables a subset of individuals to wake up at a predetermined time without referring to a watch or alarm clock. Although previous studies have indicated sleep structure as a key factor that might influence TEA during sleep, which sleep parameters could affect the TEA has not been clarified. We carried out an experimental study in which 20 healthy volunteers participated in six time estimation trials during the 9-h nighttime sleep (NS) experiment or daytime sleep (DS) experiment. The time estimation ratio (TER, ratio of the subjective estimated time interval to actual time interval) decreased significantly from the first to the sixth trial in both the NS and DS experiments. TER correlated positively with slow wave sleep (SWS) in both experiments, suggesting that SWS was a determining factor in accurate time estimation, irrespective of circadian phase they slept. No other sleep parameters showed steady influence on TEA. The present findings demonstrate that longer period of SWS is associated with the longer sleep time they subjectively experienced during sleep.

1. Introduction

Growing evidence suggests that humans have the ability to estimate the amount of time that has elapsed on the order of milliseconds to several hours (time estimation ability, TEA) even under circumstances in which external time information is not available (Morell, 1996; Harrington et al., 1998; Lalonde and Hannequin, 1999; Rao et al., 2001; Ivry and Spencer, 2004). A series of studies has supported the notion that the TEA pervades sleep period; humans perceive the amount of time that has passed during sleep (Lewis, 1969; Tart, 1970; Zung and Wilson, 1971; Bell, 1972; Moiseeva, 1975; Lavie et al., 1979; Hartocollis, 1980; Campbell, 1986; Zepelin, 1986; Hawkins, 1989; Moorcroft et al., 1997; Born et al., 1999; Kaida et al., 2003; Aritake et al., 2004; Fichten et al., 2005). This ability enables a subset of individuals to wake up at a predetermined time without referring to a watch or alarm clock. Moorcroft et al. (1997) referred to this phenomenon as "self-awakening", and Born et al. (1999) referred to it as "anticipated sleep termination". Actually, several studies have reported that more than half of individuals surveyed were able to achieve "self-awakening" with a margin of error of plus or minus 10-odd min (Lavie et al., 1979; Moorcroft et al., 1997).

A large part of the physiological mechanism of TEA remains unclear, but previous studies have shown that several physiological and psychological factors influence TEA during sleep. These include psychological status prior to bedtime (Hawkins, 1989) altered neuroendocrine tonus (Born et al., 1999), and sleep structure (Kleitman, 1963; Tart, 1970; Zung and Wilson, 1971; Lavie et al., 1979; Zepelin, 1986; Aritake et al., 2004) preceding the predetermined wake time. For instance, strong motivation and the confidence that are will wake up at the predetermined time are associated with successful self-awakening (Hawkins, 1989; Moorcroft et al., 1997). Born et al. (1999) showed clearly that anticipated awakening at a predetermined time was preceded by an elevation in ACTH secretion (a particularly early, morning ACTH surge), a phenomenon that did not occur in relation to an unexpected ("surprise") awakening at the same clock time.

Several studies have focused on sleep structure as a key factor that might influence TEA during sleep; however, it remains controversial whether the preceding sleep stage or partial

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awakening prior to the predetermined wake time modifies TEA in humans (Kleitman, 1963; Zung and Wilson, 1971; Lavie et al., 1979; Zepelin, 1986; Aritake et al., 2004). We previously conducted a study to test whether the preceding sleep structure influenced the estimated passage of time during nighttime sleep which was divided into six time periods (90 min each) in healthy young subjects (Aritake et al., 2004). We found that, as sleep progressed, the subjects underestimated the amount of time that had passed in each time period. The estimated elapsed time correlated positively with the amount of slow wave sleep (SWS) and negatively with the amount of REM sleep. These findings support the notion that TEA pervades sleep and that it is affected by the preceding sleep status.

The aim of the present study was to clarify which sleep parameters could essentially influence on TEA by comparing the properties of estimated time interval during the usual nighttime sleep (NS) period with those during an arbitrary daytime sleep (DS) period in circadian antiphase. We expected REM sleep and SWS to show different time distributions between the two experimental conditions, and that this would enable us to more precisely detect functional interaction between the sleep structure and TEA during the sleep period.

2. Materials and methods

2.1. Participants

Twenty healthy men aged 18–23 years (mean, 21.1 ± 1.7 years), who had regular sleep habits, participated in the study. They were randomly allocated to on NS experiment or DS experiment. Three participants allocated to the DS experiment withdrew from the study (one due to infection during the pre-study period, one for an undisclosed reason, and one due to discomfort during the acute shift schedule). Thus, 10 participants completed the NS experiment (mean age, 20.2 ± 1.6 years) and 7 completed the DS experiment (mean age, 22.4 ± 0.7 years). They provided written informed consent after the possible risks and details of the study were explained to them. A physician and a psychiatrist examined all participants and found that none suffered from a neurological or psychiatric disorder, and none had a history of psychoactive drug use. Participants were instructed to keep to a regular sleep–wake schedule; record their sleep patterns in a sleep log; and abstain from caffeine, nicotine, and alcohol for 1 week prior to the experiment. All participants wore a wrist activity recorder (Actiwatch-L, Mini-Mitter Co., Inc., Bend, OR, USA) for 1 week prior to the experiment. Sleep onset and offset times were determined with Actiware Sleep software (V3.2 Mini-Mitter Co., Inc.). The details recorded in participants' sleep logs, together with their sleep onset and offset times, were used to confirm that they had regular sleep–wake schedules. Because participants' attention to time could potentially affect the experimental results, we told them that the aim of the study was to investigate correlation between sleep parameters and subjective feeling; we did not disclose the study objectives until the end of the study. We confirmed that none of the participants had sensed the real purpose of the investigation until the end of this study. The study protocol was approved by the Institutional Review Board of the National Center of Neurology and Psychiatry.

2.2. Experimental procedures

Time estimation protocol is illustrated in Fig. 1.

2.2.1. NS experiment

The NS experiment was begun as follows: on day 1, the participant arrived at the laboratory at 19:00 h and slept in the laboratory bedroom from 0:00 h to 08:00 h for adaptation. After being woken at 08:00 h on day 2, the participant was kept awake until 00:00 h on day 3 under dim light conditions (150 lx). During waking hours, the participant was kept from knowing the clock time until the beginning of the time estimation protocol (TEP). His only awareness of the time of day would have been by the scheduled provision of an isocaloric meal (450 kcal) and mineral water every 4 h. At 00:00 h on day 3, the participant was instructed to go to bed and that the TEP would begin.

2.2.2. DS experiment

The DS experiment was begun as follows: on day 1, the participant arrived at the laboratory at 19:00 h and slept in the laboratory bedroom from 0:00 h to 08:00 h for adaptation. After being woken at 08:00 h on day 2, the participant was kept awake for 28 h until 12:00 h on day 3 under the same isolated condition as in the NS experiment. An isocaloric meal (450 kcal) and mineral water were provided every 4 h. After 28 h of enforced wakefulness,

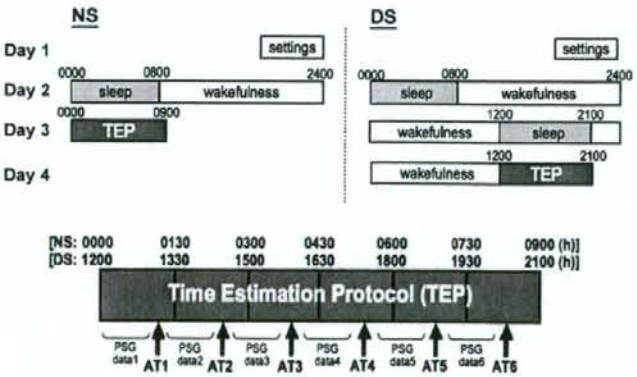

Fig. 1. Time estimation protocol (TEP). TEP was conducted between 00:00 h and 09:00 h (nighttime sleep: NS) or 12:00 h and 21:00 h (daytime sleep: DS). The 9-h polysomnography (PSG) recording periods were divided into six 90-min periods. We woke the participants and conducted a structured interview once during each 90-min period (awakening trial: AT). Participants were awakened for an AT when (1) they had slept for longer than 45 min after lights out or since the end of the prior AT; and (2) stage 2 sleep had continued for more than 3 min. PSG data between successive ATs were obtained. If these criteria were not satisfied until 75 min after the beginning of 90-min period, the participants were awakened at the end of each 90-min period. In the structured interview, we asked the several questions including, "What time do you think it is now? (subjective time of day)" to determine participants' spontaneous estimation of time, without encouraging them to focus their attention on time.

the participant was allowed recovery sleep from 12:00 h to 21:00 h on day 3. After being woken at 21:00 h on day 3, the participant was kept awake for 15 h. At 12:00 h on day 4, the participant was instructed to go to bed and that the TEP would begin.

2.3. Measures and condition

All experiments were performed in the time isolation laboratory of the National Center of Neurology and Psychiatry in Japan. Polysomnography (PSG) comprised electroencephalogram (EEG; C3–A2, C4–A1 and O1–A2, O2–A1) in conformity with the 10–20 electrode system, electrooculogram (EOG; left-A2 and right-A1), chin surface electromyogram (chin-EMG), and electrocardiogram (ECG) recordings. PSG data were obtained continuously during each experiment and stored in a digital EEG system (Neurofax, Nihon Kohden, Tokyo, Japan). Core body temperature (cBT) was measured every 2 min from 21:00 h on day 1 until the end of the experiment, the data were stored in a soft ware (V3.2 Mini-Mitter Co., Inc.). The PSG and cBT monitoring were set up between 19:00 h and 21:00 h on day 1. The participant' behavioral status and sleep–wake status were continuously monitored by two well-trained research attendants using a digital EEG system and by visual observation. Room temperature and humidity were controlled at 24 °C and 60%, respectively.

2.4. Time estimation protocol

The 9-h PSG recording period was divided into six 90-min periods (Fig. 1). During each 90-min period, the participant was awakened and given a brief structured interview with supine (lasting 2 min or less, <8 lx) about the perceived clock time. This procedure was termed the awakening trial (AT). The time of each AT was determined when (1) the participant had slept for more than 45 min after lights-out or since the end of the prior AT; and (2) stage 2 sleep had continued for more than 3 min. If these criteria were not satisfied before 75 min of each 90-min period has passed, the participant was awakened at the end of the 90-min period. During the structured interview, we asked several questions including, "What time do you think it is now?" to determine the participant's spontaneous estimation of time, without encouraging him to focus his attention on the amount of time that had passed since previous arousal. The interviewer was instructed not to give disclose the real purpose of the study, and the participant was given no information on the exact number or timing of the ATs.

2.5. Data analysis

2.5.1. TEA variables

The subjective time interval, defined as the difference between the estimated time of day during the AT and that during the previous AT (or 00:00 h) was determined. Time estimation ratio (TER), defined as the estimated time interval (subjective time interval: s_1 or s_2) divided by the actual clock time interval (actual time interval: a_1 or a_2) (Aritake et al., 2004) (Fig. 2), was also determined.

2.5.2. Sleep parameters

PSG data obtained between successive ATs were scored in epochs of 30 s according to the standard criteria (Rechtschaffen and Kales, 1968). Time percentages of stage W (%stage W), stage 1 (%stage 1), stage 2 (%stage 2), stage 3 + 4 (%stage 3 + 4) and stage REM (%stage REM) sleep for the entire sleep period and for each AT period were calculated for all PSG recordings.

2.5.3. cBT

To ensure comparability of the circadian phase between the NS and DS experiments, we determined the times of nadir and peak time of cBT in both experiments. The cBT data from 18:00 h on day 2 to 24:00 h on day 3 was smoothed by using a 24-h double cosine curve fit procedure (Kaleida Graph ver.3.6, Hulinks Inc., Tokyo, Japan) for both the NS and DS experiments, and the times of the fitted minimum (nadir) and maximum (peak time) of cBTs were determined.

2.6. Statistical analyses

Differences in variables between the NS and DS experiments were analyzed by *t*-test. Differences in TEA variables for each AT between the NS and DS experiments were analyzed by two-way repeated measures ANOVA (ATs × NS vs. DS) or two-way factorial ANOVA (sleep stages just before ATs × NS vs. DS). Correlations

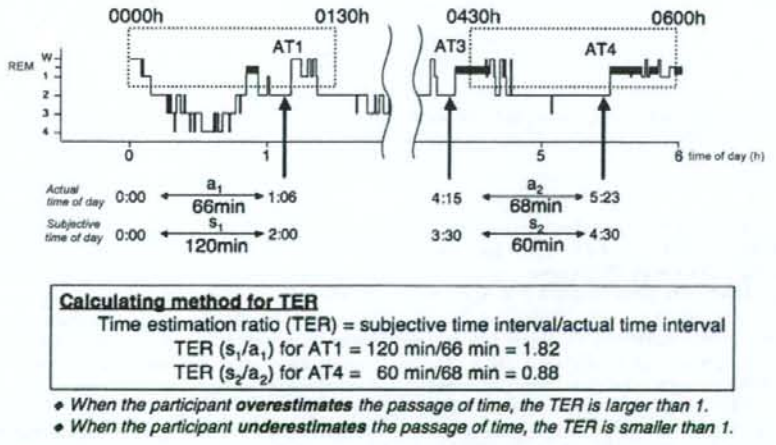

Fig. 2. Time estimation ratio (TER). Subjective time interval in both experiments was defined as the time difference between subjective times of the day, which were obtained at successive awakening trials (ATs). The actual time interval was defined as the actual time difference between successive ATs. The TER, as an indicator of subjective time estimation, was calculated by the dividing a subjective time interval (s_1 or s_2) by the actual time interval (a_1 or a_2).

Table 1
Sleep and core body temperature parameters in normal NS and DS.

	NS (n = 10) (mean ± S.D.)	DS (n = 7) (mean ± S.D.)	t-Test (p-value)
Total recording time (min)	484.5 ± 25.7	502.1 ± 20.0	n.s.
Total sleep time (min)	436.9 ± 46.8	348.3 ± 56.9	0.003
Sleep efficiency (%)	90.5 ± 10.6	69.6 ± 12.9	0.002
Wake (min)	47.5 ± 55.9	153.8 ± 68.1	0.003
Stage 1 (min)	40.2 ± 19.0	48.8 ± 19.6	n.s.
Stage 2 (min)	240.1 ± 40.6	187.9 ± 42.1	0.021
Stage 3 + 4 (min)	58.8 ± 21.9	45.4 ± 9.5	n.s.
REM (min)	65.5 ± 31.9	59.00 ± 10.1	n.s.
Wake (%)	9.5 ± 10.6	30.4 ± 12.8	0.002
Stage 1 (%)	8.3 ± 3.9	9.8 ± 4.0	n.s.
Stage 2 (%)	49.7 ± 9.1	37.6 ± 9.3	0.017
Stage 3 + 4 (%)	12.1 ± 4.5	9.0 ± 1.7	n.s.
REM (%)	13.5 ± 6.6	11.8 ± 2.1	n.s.
Core body temperature parameters			
Nadir time (h)	5.5 ± 1.3	6.3 ± 2.3	n.s.
Peak time (h)	18.9 ± 2.9	20.36 ± 4.1	n.s.

p = probability, n.s. = not significant.

between variables were assessed by Pearson's correlation coefficient. Stepwise multiple regression analysis was used to evaluate relationship between TEA variables (dependent variables) and sleep structures or circadian phase (predictor variables). StatView ver.5.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Data were expressed as mean ± standard deviation. The level of significance was set at $p < 0.05$.

3. Results

3.1. PSG variables

PSG variables for the entire sleep period in the NS and DS experiments are shown in Table 1. There was no significant difference in total recording time between the two experiments. Total sleep time and sleep efficiency in the DS experiment were significantly deceased in comparison to corresponding values in the NS experiment. There were no significant differences in total duration and percentages of stage 1, stage 3 + 4, or stage REM sleep between the two experiments. However, sleep total duration and percentage of stage W sleep were significantly increased and those for stage 2 sleep were significantly decreased in the DS experiment in comparison to corresponding values in the NS experiment.

3.2. Circadian phase

There was no significant difference in the time of nadir or peak time of cBT between the NS and DS experiments (Table 1).

3.3. AT variables

PSG stages during which ATs were carried out differed between the NS and DS experiments; 91.67% and 64.29% ATs, respectively, were carried out in stage 2, 6.67% and 11.1% ATs were carried out in stage 1, and 1.67% and 44.44% ATs were carried out in stage W. However, two-way factorial ANOVA (sleep stage just before ATs × NS vs. DS) revealed that there was no significant main effect of sleep stages just before ATs on TER ($F(2, 96) = 1.615$, $p = 0.204$); neither was there a significant main effect of experimental condition ($F(1, 96) = 0.908$, $p = 0.343$) nor a significant interaction ($F(2, 96) = 0.076$, $p = 0.927$) between sleep stages just before ATs and experimental condition. Therefore, the TER data obtained in the three different PSG stages (stages 1, 2, and W) were combined in further analyses.

3.4. TER

There was no significant difference in the TER for the entire sleep period between the NS and DS experiments (NS experiment, 0.966 ± 0.717; DS experiment, 1.006 ± 0.747). Time course of the TER and the percentages of sleep stages are shown in Fig. 3. Two-way repeated measures ANOVA (ATs × NS vs. DS) revealed a significant main effect of the time course on TER ($F(5, 75) = 13.254$, $p < 0.0001$), whereas there was neither a significant main effect of experimental condition ($F(1, 75) = 0.110$, $p = 0.745$) nor a significant interaction ($F(5, 75) = 0.326$, $p = 0.896$) between time course and experimental condition. The TER value was at nearly two during AT1 and gradually decreased toward 0.5 as sleep progressed. The pattern was similar in the NS and DS experiments (Fig. 3a).

3.5. Sleep structures

Two-way repeated measures ANOVA (ATs × NS vs. DS) revealed a significant main effect of time course on stage 3 + 4 ($F(5, 75) = 12.285$, $p < 0.001$), whereas there was neither a significant main effect of experimental condition ($F(1, 75) = 2.266$, $p = 0.153$) nor a significant interaction ($F(5, 75) = 0.144$, $p = 0.981$) between time course and experimental condition (Fig. 3d). Two-way repeated measures ANOVA (ATs × NS vs. DS) also revealed a significant main effect of time course on %stage 3 + 4 ($F(5, 75) = 18.333$, $p < 0.001$), whereas there was neither a significant main effect of experimental condition ($F(1, 75) = 2.436$, $p = 0.139$) nor a significant interaction ($F(5, 75) = 0.184$, $p = 0.968$) between time course and experimental condition. The stage 3 + 4 decreased as sleep progressed in both the NS and DS experiments (Fig. 3i).

There was a significant interaction between time course and conditions in stage REM, stage W, and stage 2. Stage REM in NS increased toward morning, whereas stage REM in DS decreased toward nighttime. Stage W in NS did not change toward morning, whereas stage W in DS increased from AT5 to AT6. Stage 2 in NS did not change toward morning, whereas stage 2 in DS decreased from AT5 to AT6 (Fig. 3b, c and e). No significant effect of time course was found in stage 1 in either two conditions. We also found comparable results in corresponding percentage values for all sleep stages (Fig. 3g, h and j).

3.6. Correlation between TER and sleep structures

We averaged the TER and stage 3 + 4 sleep per AT data across all participants to reduce inter-individual variation in sleep

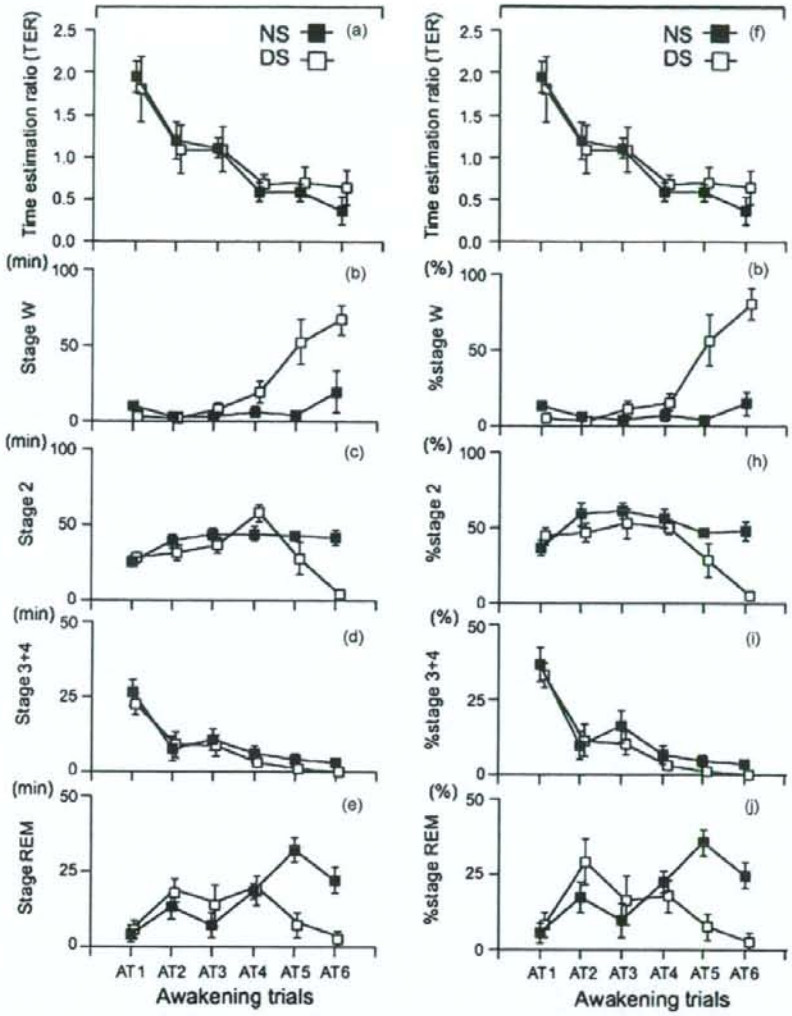

Fig. 3. (a–j) Time course of the mean time estimation ratio (TER) and the amounts (left panel) and the percentages (right panel) of sleep stages. Filled and open circles represent the data in nighttime sleep (NS) and daytime sleep (DS) experiments, respectively. The horizontal axes indicate the AT number. Two-way repeated measures ANOVA revealed a significant main effect of time course on TER and stage 3 + 4 sleep in both experiments. The value of TER was nearly 2.0 at AT1, and it decreased toward 0.5 as sleep progressed.

structure. Significant positive correlation was found between averaged TER and averaged stage 3 + 4 in both the NS ($r = 0.943$, $p = 0.002$) and DS ($r = 0.993$, $p < 0.001$). We also found a significant positive correlation between the averaged TER and averaged %stage 3 + 4 in both the NS ($r = 0.944$, $p = 0.002$) and DS ($r = 0.993$, $p < 0.001$).

3.7. Stepwise multiple regression analysis for TER

The following variables were analyzed by stepwise multiple regression for prediction of TER (dependent variable): stage W, stage 1, stage 2, stage 3 + 4, stage REM, and acrophase of each AT (interval between the time of cBT nadir and the time of each AT). Only stage 3 + 4 was identified as a predictive variable that explained the variance of TER ($r = 0.251$, $p = 0.011$). We also found comparable results in percentage values for sleep stages; only %stage 3 + 4 was identified as a more prominent predictive variable that explained the variance of TER ($r = 0.327$, $p = 0.001$).

4. Discussion

In the present study, we investigated influences of the sleep architecture on TEA during NS and DS periods. We found that TER, as an indicator of a subjectively estimated time interval, was higher at the beginning of the sleep period (i.e., sleep time was overestimated than the actual time elapsed), and that it successively decreased toward the end of the sleep. Positive correlation between the amount of SWS and the TER was confirmed in both the NS and DS periods, despite the fact that the two sleep periods were located around the circadian antiphase

represented by the cBT. This suggests that the greater the amount of SWS the study subjects obtained, the longer the sleep time they subjectively experienced. We could not confirm a steady influence of REM sleep on TEA in our study participants. We observed negative correlation between the amount of REM sleep and the TER only in the NS period, as was reported previously (Aritake et al., 2004). This relation disappeared in the DS period during which the normal REM sleep pattern was distorted (Weitzman et al., 1980; Dijk and Czeisler, 1995; Borbely and Achermann, 1999). Comparison of sleep structures and TER properties between the NS and DS periods clearly highlighted the significant influence of SWS on TEA in humans.

The study subjects experienced poorer sleep continuity (shorter total sleep time, decreased sleep efficiency, and longer awake time) in the DS period than in the NS period, possibly due to the circadian antiphase, although the amounts of stage 1, stage 3 + 4, and stage REM sleep did not differ significantly between the two experimental conditions. However, it is not likely that the differences in sleep structure during the 9-h PSG recording period substantially influenced the relation between the sleep architecture and TEA because similar TER values close to 1 were obtained (0.966 ± 0.72 for the NS period, 1.006 ± 0.75 for the DS period), suggesting that participants could accurately estimate the length of sleep time (on average) through the entire sleep period.

While the underlying regulatory mechanism of TEA during sleep remains to be clarified, various brain sites have been revealed to be responsible for human TEA of different temporal range (Ivry, 1996; Lalonde, 1999; Lewis and Miall, 2003; Ivry, 2004). For instance, the cerebellum is reported to be involved in the short time estimation of less than 1 s (Jueptner et al., 1995; Rao et al., 1997; Spencer et al., 2003; Ivry and Spencer, 2004). Contrastingly, the prefrontal cortex is involved in the time estimation of more than 1 s (Mangels et al., 1998; Lalonde and Hannequin, 1999; Lewis and Miall, 2003). Concerning the TEA during sleep, greater cortical deactivation during a longer period of SWS might contribute to overestimation of the actual sleep time. Kajimura et al. (1999) studied cerebral blood flow during sleep by means of positron emission topography. Sleep-induced cortical deactivation started during light stages of nocturnal sleep and progressed in a sleep stage-dependent manner; cerebral blood flow during deep non-REM sleep was reduced in the midbrain, basal forebrain, and basal ganglia (caudate nucleus) and bilaterally in neocortical regions including the medial and inferior frontal gyrus. During wakefulness, the cerebellum, the prefrontal cortex and basal ganglia perform higher-order processing of sensory information, integrating cognitive information. Several neuroimaging studies in humans have shown that the cerebellum, the prefrontal cortex and a corticostriatal network in the basal ganglia are responsible for the ability to perceive time intervals during wakefulness (Jueptner et al., 1995; Maquet et al., 1996; Rao et al., 1997, 2001; Harrington et al., 1998; Pouthas et al., 1999; Gruber et al., 2000; Schubotz et al., 2000; Spencer et al., 2003; Coull et al., 2004). These neuronal systems might also contribute to the regulation of TEA during sleep. Thus, preceding deep sleep and associated cortical deactivation could substantially influence perceived passage of time during sleep.

During wakefulness, TEA has been reported to show diurnal fluctuation (Aschoff, 1998; Campbell et al., 2001; Kuriyama et al., 2005). A study involving a time production strategy (producing a predetermined time interval by pressing a button) during wake time has shown that TEA might be influenced by the circadian system in humans (Kuriyama et al., 2005). The produced time interval tended to be shorter than the actual time interval during the nighttime, and it became longer toward the morning time. This is analogous to individuals overestimating the perceived time interval in the first half of rather than the latter half of the sleep period, as was observed in our present study. However, in our study subjects, changes in TER for the NS and DS periods in reciprocally circadian antiphase showed remarkably similar time profiles and multiple stepwise regression analysis revealed no relation between acrophases of time estimation and the corresponding TER values. Although we examined the change in TEA for only 8–9 h of each sleep periods, our findings do not support the notion that the TEA during sleep time was primarily under the regulation of circadian system.

These findings were obtained using a time estimation protocol consisted of six 90-min period interval trials, which might interfere in the naturalistic sleep cycle including REM–NREM sleep cycles and TEA properties in the study subjects. Despite of the limitations, the present study support the notion that humans possess the TEA that pervades sleep period and that SWS can prolong the subjectively estimated time interval during sleep, irrespective of the circadian phase they slept. Future studies should focus on the physiological mechanism of TEA during sleep and reveal the pathophysiological features of TEA in several sleep disorders such as paradoxical insomnia in which subjective sleep disturbances appear without objective evidence of deteriorated sleep quality (Salin-Pascual et al., 1992; Edinger and Fins, 1995; Perlis et al., 1997; Vanable et al., 2000; ICSD, 2005; Edinger and Krystal, 2003). Time estimation protocol we applied in this study would be an useful option in the human sleep studies.

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Original article

Association between subjective well-being and sleep among the elderly in Japan

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Abstract

Objective: The purpose of this study was to examine the association between sleep and subjective quality of life in an elderly Japanese population.
Methods: Elderly people aged 70 years or more ($n = 1769$) were selected randomly from all areas of Japan. They were visited and interviewed in November 2003. Subjective well-being of the subjects was assessed using the Philadelphia Geriatric Center (PGC) Morale Scale. A logistic regression analysis was performed using sleep-related factors as explanatory variables.
Results: A positive linear association was observed between subjective sleep sufficiency and the mean PGC Morale Scale score. The crude and adjusted odds ratios for sleep disorders such as difficulty initiating sleep, excessive daytime sleepiness, and restless legs syndrome were significantly low. The mean score was highest for a sleep duration of 7–8 h and became lower at sleep durations of <6 and ⩾9 h (inverted U-shaped association). However, the adjusted odds ratio for sleep duration did not show a significant reduction.
Conclusions: In order to improve the subjective well-being of the elderly, better subjective sleep sufficiency and alleviation of sleep disorders are necessary. Different mechanisms may reduce subjective well-being in individuals who sleep less than 6 h or who sleep 9 h or more.

Keywords: Subjective well-being; PGC Morale Scale; Subjective sleep sufficiency; Sleep disorders; Sleep duration; Elderly in Japan

1. Introduction

Since sleep disorders have been recognized as an important public health issue in developed countries, various epidemiological studies have been conducted. Among the elderly, insomnia is a common complaint. According to a survey targeting the general adult Japanese population, 29.5% people aged 60 years or more complained of insomnia [1]. The survey revealed that in comparison with young people, the number of elderly affected by early morning awakening (EMA) or difficulty maintaining sleep (DMS) was greater [1,2]. It is considered that shallow sleep caused by aging as well as physical factors such as nocturia and physical pain induce DMS in the elderly [3]. As a result of the rapid aging of Japanese society, sleep disorders among the elderly will reduce the quality of life (QOL) and become an increasingly serious issue in the future.

Conventionally, subjective well-being has been measured for assessment of QOL in the field of healthcare

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for the elderly [4]. However, no study has yet examined the associations between subjective well-being and sleep. Sleep disorder is recognized as being closely associated with depression [5,6], and a report has suggested that there is a significant association between depression and subjective well-being [7]. Thus, examination of the association between subjective well-being and sleep is considered useful. Therefore, we examined the associations between subjective well-being and subjective sleep sufficiency, sleep disorders, and sleep duration among the elderly.

2. Subjects and methods

Nihon University Center for Information Networking has conducted a longitudinal study entitled "A Survey on Health and Lifestyle" [8]. The subjects comprised 4995 people aged 65 years or more, selected from all areas of Japan by stratified two-step random sampling. First, the sample size was established on the basis of the estimated national population within this age bracket in November 1999. Individuals aged 75 or more were doubly sampled and weighted in the calculation to ensure that the results adequately represented the elderly population of Japan.

The baseline survey was carried out in November 1999. After obtaining informed consent from the subjects, well-trained interviewers interviewed the subjects at their homes. Similar interviews were repeatedly conducted on the same subjects in November 2001 and November 2003.

The present study used only the data of a cross-sectional study conducted in November 2003. People aged 70 years or more (3248) were selected as participants (Table 1a). After eliminating participants who omitted even one answer (including those who answered "I don't know"), the data for the remaining 1769 (54.5%) were analyzed (Table 1b).

Questions from the 11-item version of the Philadelphia Geriatric Center (PGC) Morale Scale [9,10] were included in the questionnaire as indicators of subjective QOL [11]. Scoring was performed in compliance with the conventional method, and a total score was obtained [9]. Subjective well-being is judged to be better if the scores are higher.

The subjects were divided into two groups according to the PGC Morale Scale total scores. Subjects with total scores of 9 or higher (9 being the median of the total PGC Morale Scale scores) were included in the high group, and those with scores of less than 9 were included in the low group. To investigate the factors that influence subjective well-being, crude and adjusted odds ratios and 95% confidence intervals were calculated by employing univariate and multivariate logistic regression models in which the high and low groups were used as response variables.

Table 1a
Numbers of subjects classified by age group and gender (original participants)

Gender	Age (year)				
	70–74	75–79	80–84	85&over	Total
Men	441	353	365	206	1365
Women	445	450	595	393	1883
Total	886	803	960	599	3248

Table 1b
Numbers of subjects classified by age group, PGC Morale Scale score, and gender (final participants)

Gender	PGC MS#	Age (year)				
		70–74	75–79	80–84	85 over	Total
Men	High	177	126	105	45	453
	Low	103	86	82	45	316
Women	High	161	150	149	73	533
	Low	115	114	164	74	467
Total		556	476	500	237	1769

#: PGC Morale Scale: high ≧9, low <9.

The following data were obtained as socio-demographic factors: age, gender, present place of residence (urban/rural), and educational history in four grades (junior high school, including primary school under the old education system; high school, including middle school under the old educational system; vocational school or college; and university, including high school under the old education system and graduate school). Educational history was categorized using an ordinal scale from 1 to 4.

First, the association between subjective sleep sufficiency and subjective well-being was examined. We then examined the associations of each of six sleep disorders (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS], early morning awakening [EMA], sleep-enhancing medication use [SEMU], excessive daytime sleepiness [EDS], and restless legs syndrome [RLS]) with subjective well-being. The manner in which associations between the sleep disorders and subjective well-being were modified by various factors, such as subjective sleep sufficiency and self-rated health, was also examined.

Subjects were interviewed regarding their conditions during the past month. The question pertaining to subjective sleep sufficiency was "Do you obtain sufficient rest during sleep?" The following were the four optional answers to this question: (1) very sufficient, (2) sufficient, (3) insufficient, and (4) very insufficient. These four categories were regrouped into the following two categories: sufficient (1 + 2) and insufficient (3 + 4).

As to the questions on sleep disorders, in line with the questionnaires used in the previous studies [1,2,12–15], the following six questions were used in the present study:

1. "Do you have difficulty falling asleep at night?" (DIS)
2. "Do you wake up during the night after you have gone to sleep?" (DMS)
3. "Do you wake up too early in the morning and have difficulty getting back to sleep?" (EMA)
4. "Do you take any medications or use alcoholic beverages to help you sleep?" (SEMU)
5. "Do you feel excessively sleepy during the day?" (EDS)
6. "Is your sleep interrupted by a creeping sensation or hot flushes in your legs after you go to bed at night?" (RLS)

The following were the five optional answers to these questions: (1) never, (2) seldom, (3) sometimes, (4) often, and (5) always. These five categories were regrouped into the two categories: no (1 + 2) and yes (3–5).

In addition, the question pertaining to physical pain was "Do you often suffer from physical pain?" The optional answers were yes and no. The question pertaining to psychological stress was "Do you currently feel stress in your daily life?" The optional answers were yes and no. Regarding self-rated health, the question posed was "In general, how is your current health condition?" The three optional answers were good, fair, and poor [16].

The following criteria were used as covariates in the logistic regression model: age, gender, present place of residence, education history, sleep duration, six sleep disorders, physical pain, psychological stress, subjective sleep sufficiency, and self-rated health. For multivariate analyses, the following three models were created: a model in which subjective sleep sufficiency was not included among the covariates (Model 1), a model in which subjective sleep sufficiency was included (Model 2) among the covariates, and a model in which self-rated health was further included among the covariates (Model 3). All variables were applied to each model.

Based on nocturnal sleep duration, the subjects were divided into the following five categories based on their answers to the question "What is your daily average sleep duration (excluding the duration of naps)?": less than 6 h (<6 h), 6 h or longer but less than 7 h (6–7 h), 7 h or longer but less than 8 h (7–8 h), 8 h or longer but less than 9 h (8–9 h), and 9 h or longer (≥9 h). As shown in Table 4, several models were created to examine the associations between subjective well-being and sleep duration by using different combinations of the following covariates: socio-demographic factors plus six sleep disorders, psychological stress, physical pain, subjective sleep sufficiency, and self-rated health.

For statistical analyses, SAS (PC version, Ver. 8e) was employed. A variable having three or more categories was treated as a dummy variable in the analyses. The Kruskal–Wallis test and Bonferroni's correction for multiple comparisons were performed for comparison of multiple groups, and the Wilcoxon rank-sum test was performed for comparison of two groups. The level of significance was set at 5%.

3. Results

The numbers of respondents according to gender and age are shown in Tables 1a and 1b. The number of participants was 1769 (769 males (43.4%) and 1000 females (56.5%)).

Comparisons of participants' attributes and the mean PGC Morale Scale scores are shown in Table 2. The mean PGC scores decreased as age increased. The mean score for males was higher than that for females. No difference was observed with regard to current place of residence. The mean PGC score increased significantly with improved educational history. Every sleep disorder was significantly associated with the PGC score. With regard to the mean scores calculated by taking into consideration sleep duration, the mean score was highest for a sleep duration of 7–8 h. The mean scores were significantly lower for sleep durations of <6 and ≥9 h.

The association between subjective sleep sufficiency and the mean values of PGC scores is shown in Fig. 1. As subjective sleep sufficiency ameliorated, the mean values increased. A positive linear association was observed between subjective sleep sufficiency and PGC score.

The mean PGC Morale Scale scores plotted against sleep duration are shown in Fig. 2. The mean value was highest for a sleep duration of 7–8 h, and was decreased for sleep durations of <6 and ≥9 h, giving an inverted U-shaped association. There were significant differences between the mean PGC scores for sleep durations of 7–8 h and <6 h and those for sleep durations of 7–8 and ≥9 h.

The results of logistic regression analysis with regard to the associations of the PGC Morale Scale scores with socio-demographic indices and sleep-related factors are shown in Table 3. With regard to age, the odds ratio of PGC scores for subjects aged 70–74 years was used as a reference. No significant difference was recognized when comparing the adjusted odds ratios of other age groups with the reference. Similarly, no significant difference was recognized among the adjusted odds ratios for gender. However, with regard to educational history, as observed in the comparison of the mean PGC scores, the adjusted odds ratios also showed a significant association. The adjusted odds ratios for the PGC scores increased with improved educational history.

The influences of adjustments when the covariates of sleep disorders were used in the analyses are shown in Table 3. The crude odds ratios with regard to PGC scores showed significant associations with sleep disorders and the adjusted odds ratios with regard to PGC scores for DIS, EDS, and RLS were significantly lower