Table 1
Clinical characteristics of patients.

Patient no.	Age (years)	Gender	Diagnosis (DSM-IV)	Dose of sulpiride (mg)	Duration of illness (years)	PANSS			
						Positive	Negative	General	Total
1	32	M	295.30	1200	15	16	21	30	67
2	45	F	295.30	600	28	25	26	49	100
3	47	M	295.30	1200	8	18	23	44	85
4	47	M	295.30	1000	25	23	26	47	96
5	52	M	295.10	1200	5	13	33	46	92
6	56	M	295.60	600	29	20	43	59	122
Mean ± SD	46.5 ± 8.2			966.7 ± 294.4	18.3 ± 10.5	19.2 ± 4.4	28.7 ± 8.1	45.8 ± 9.4	93.7 ± 18.1

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; PANSS, Positive and Negative Scale for Schizophrenia; M, Male; F, Female.

met the criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) for diagnosis of schizophrenia. The diagnosis was assessed by Structured Clinical Interview for DSM-IV by three psychiatrists. The patients underwent general medical and laboratory evaluation. Organic brain disease was ruled out by CT, T1-weighted magnetic resonance (MR) images, and electroencephalogram.

Prior to this study, they had been prescribed antipsychotics during the periods indicated as 'duration of illness' in Table 1. In chlorpromazine equivalents, daily doses ranged from 200 mg to 606 mg and mean dose was 384 ± 139 mg/day (Inagaki and Inada 2006).

In all patients, the previously used antipsychotic drugs were changed to sulpiride, a selective dopamine D_2/D_3 receptor antagonist without affinity to dopamine D_1 receptor. PET scans were performed after a washout period of at least three weeks after changing to sulpiride. Sulpiride was maintained at the same dosage during the washout period. Because of extrapyramidal side effects, two patients were administered a relatively low dose of sulpiride (600 mg), although there had been no exacerbation of their psychic symptoms. All patients underwent clinical ratings of their psychopathology using the positive and negative syndrome scale (PANSS; Kay et al. 1987), and the following cognitive function tests: Wisconsin Card Sorting Test (Heaton 1981) to evaluate executive function, Stroop test (Cohen and Servan-Schreiber 1992) and *n*-back tasks (2-back minus 0-back using letters as stimulus; Cohen et al. 1994; Owen et al. 2005) to evaluate working memory.

The healthy control sample consisted of 6 females and 6 males, age-matched at 42.8 ± 8.5 years. Based on unstructured psychiatric screening interviews, none had a history of neurological or psychiatric illness. Organic brain disease was ruled out by T1-weighted MRI.

The study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan. After providing a complete explanation of the study, written informed consent was obtained from all subjects.

PET and MRI procedures

All patients except patient #6 (Table 1) underwent both PET scans using [^{11}C]NNC112 and [^{11}C]SCH23390 on the same day. Patient #6 and twelve healthy controls underwent each of the PET scans with [^{11}C]NNC112 and [^{11}C]SCH23390 within several days. The PET system ECAT EXACT HR+ (CT1-Siemens, Knoxville, TN) was used for all PET studies. The system provides 63 planes with a 15.5 cm axial field of view. After a transmission scan with a ^{68}Ge–^{68}Ga source, a bolus of [^{11}C]NNC112 or [^{11}C]SCH23390 was rapidly injected into the antecubital vein with a 20-ml saline flush. Injected radioactivity and specific radioactivity were 220.5 ± 9.25 MBq and 140.0 ± 64.1 GBq/μmol for patients in the [^{11}C]NNC112 studies, 215.0 ± 14.1 MBq and 152.5 ± 50.6 GBq/μmol for controls in the [^{11}C]NNC112 studies, 200.2 ± 15.9 MBq and 59.7 ± 15.5 GBq/μmol for patients in the [^{11}C]SCH23390 studies, and 220.5 ± 18.1 MBq and 68.6 ± 11.0 GBq/μmol for controls in the [^{11}C]SCH23390 studies, respectively.

Radioactivity in the brain was measured by a series of scans for 90 min for [^{11}C]NNC112 or 60 min for [^{11}C]SCH23390, starting immediately after the injection. During image acquisition, the subjects were instructed to lie quietly with their eyes closed and earplugs in place. Image reconstruction was performed with a Hanning filter with a cut-off frequency of 0.4, a value experientially determined for the purpose of noise reduction, resulting in a final spatial resolution of 7.5 mm FWHM (full width at half maximum).

T1-weighted MR images were acquired on Philips Gyroscan NT, 1.5 T (Philips Medical Systems, Best, The Netherlands). Scan parameters were 1-mm-thick 3D images with a transverse plane (repetition time, TR/echo time, TE 21/9.2 ms, flip angle 30°, matrix 256 × 256, field of view (FOV) 256 × 256), yielding 196 contiguous slices of the head.

PET data analysis

Regions of interest (ROIs) were manually drawn on the transverse slices from each subject's PET summation images referred from MRI images coregistered to the reconstructed PET images. ROIs were set to cover 3 adjacent slices for the striatum including both the caudate nucleus and the putamen, anterior cingulate, cerebellum, temporal cortex and frontal cortex including the superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus, which roughly corresponds to dorsolateral prefrontal cortex. The sets of ROIs for each section were transferred to the corresponding PET images, and time–activity curves (TACs) were obtained. The TACs of each region were analyzed using a simplified reference tissue model in a least-squares manner, in which the cerebellum was used as reference tissue (Lammertsma and Hume 1996). This procedure produced the binding potential (BP_{ND}; Innis et al. 2007) value.

Statistical analysis

Statistical analysis of the regional BP_{ND} obtained from patients with schizophrenia and healthy control subjects was performed using one-way analysis of covariance (one-way ANCOVA) with age as covariate using SPSS for Windows 16.0.2J (SPSS Inc, Chicago, Illinois, USA 2008), and post hoc Bonferroni correction was used for multiple comparisons. p value $< 0.05/4 = 0.0125$ was considered significant.

Results

Table 1 lists the clinical profiles of the patients. The average duration of illness after schizophrenia diagnosis was 18.3 years. Scores of the two cognitive functional tests are shown in Table 2, and significant group effects were found in each cognitive function test. Because four patients, #2, #3, #5 and #6, were not able to do *n*-back task (2 back), results were not shown in Table 2.

Significant correlations between BP_{ND} and age were observed in patients with [^{11}C]NNC112 (frontal cortex, $r = -0.924$, $p = 0.004$; striatum, $r = -0.981$, $p = 0.001$), controls with [^{11}C]NNC112 (striatum, $r = -0.886$, $p < 0.001$) and controls with [^{11}C]SCH23390 (frontal cortex, $r = -0.757$, $p = 0.004$; striatum, $r = -0.700$, $p = 0.011$). Trend

Table 2
Cognitive task scores of patients.

Patient no.	W-CST			Stroop test	
	Category	PEN	DMS	Error	Time score
1	6	0	0	0	17.4
2	2	9	5	11	46.6
3	1	7	3	1	7.4
4	5	1	1	0	5.4
5	2	14	0	2	68
6	Incapable	Incapable	Incapable	2	75
Mean ± SD	3.2 ± 2.2	6.2 ± 5.8	1.8 ± 2.2	2.7 ± 4.2	36.6 ± 30.8
Controls					
Mean ± SD	4.7 ± 1.6	1.4 ± 2.0	0.8 ± 1.4	0.8 ± 1.2	5.6 ± 4.0

W-CST, Wisconsin card sorting test; PEN, errors of nelson; DMS, difficulty in maintaining set.

level correlations were observed in other regions and patients with [^{11}C]SCH23390.

All BP_{ND} values of both ligands are shown in Fig. 1 and summarized in Table 3. ANCOVA with age as covariate ($df = 1,15$) of BP_{ND} values of all ROIs revealed that the patient group showed significantly lower BP_{ND} value compared with the control group in both ligands ([^{11}C]NNC112: temporal cortex, $F = 26.24$, $p < 0.001$; striatum, $F = 60.08$, $p < 0.001$; anterior cingulate cortex, $F = 9.14$, $p = 0.009$; frontal cortex, $F = 42.96$, $p < 0.001$, [^{11}C]SCH23390: temporal cortex, $F = 34.68$, $p < 0.001$; striatum, $F = 25.46$, $p < 0.001$; anterior cingulate cortex, $F = 8.91$, $p = 0.009$; frontal cortex, $F = 37.60$, $p < 0.001$). There was significant correlation between average BP values of [^{11}C]NNC112 weighted by ROI size and that of [^{11}C]SCH23390 ($r = 0.859$; $BP_{NNC} = 0.613\ BP_{SCH} + 0.0414$).

There was no significant correlation between BP_{ND} values and doses of antipsychotic drugs and between BP_{ND} values and PANSS scores for positive symptom, negative symptom, general symptom and total score in any of the brain regions.

Discussion

Both [^{11}C]NNC112 and [^{11}C]SCH23390 bindings in the striatum and cortical regions of patients with schizophrenia in severe residual phase were significantly lower compared with healthy controls. In previous PET studies of patients with schizophrenia who were antipsychotics-naïve or -free, BP of [^{11}C]SCH23390 was decreased (Okubo et al. 1997) or unchanged (Karlsson et al. 2002), and was increased when measured by [^{11}C]NNC112 (Abi-Dargham et al. 2002). Several differences in those studies have been discussed, including those regarding duration of illness, medications, race, severity of symptoms and radioligands. Guo et al. (2003) reported different characteristics of in vivo binding of the two radioligands in rat brain, increased [^{11}C]NNC112 binding and decreased [^{3}H]SCH23390 binding, following subchronic dopamine depletion with reserpine. But the inconsistent results cannot be explained solely by the difference of radiotracers, and demographics of patients might have been contributing factors.

Although [^{11}C]SCH23390 and [^{11}C]NNC112 are selective radioligands for dopamine D_1 receptor, both ligands have some affinity for 5-

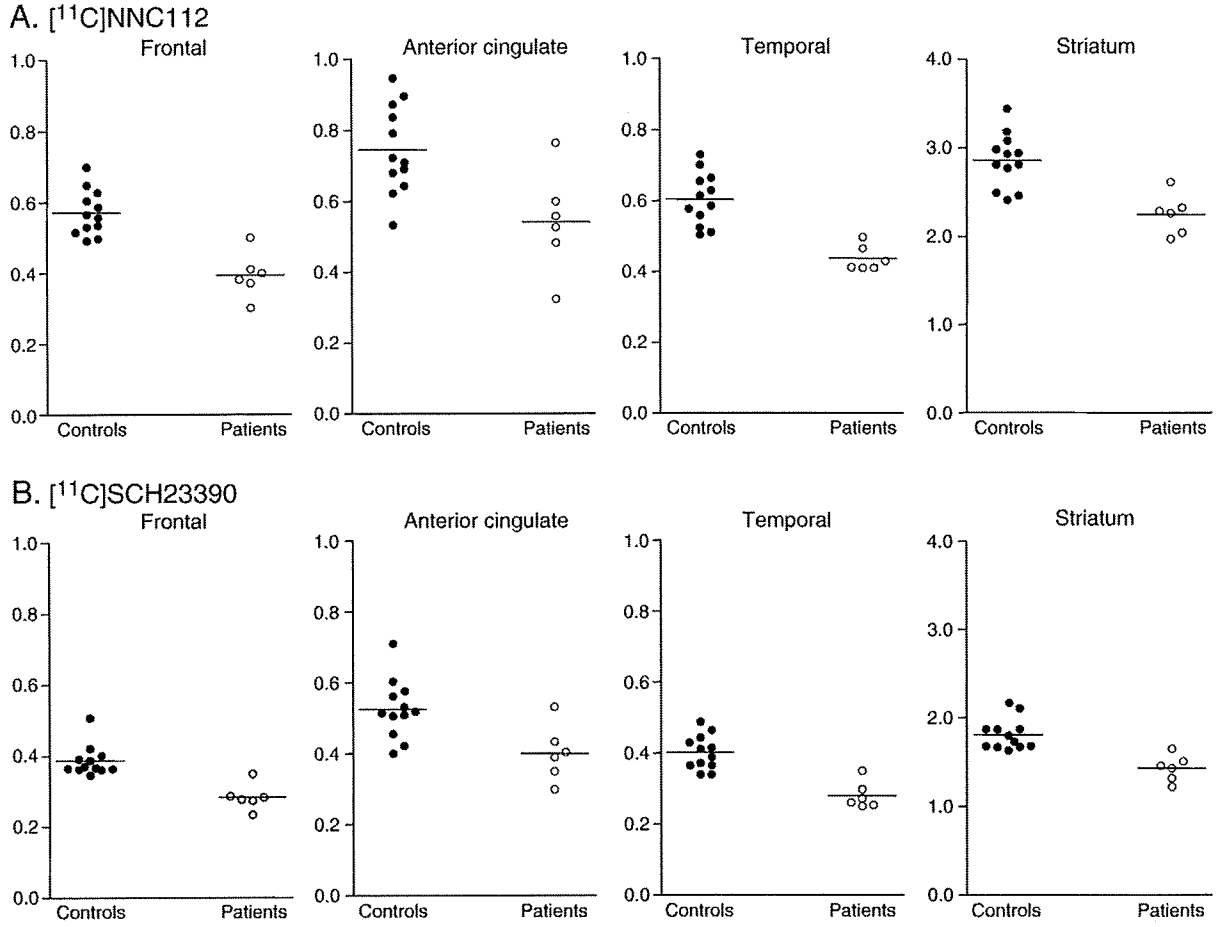

Fig. 1. BP_{ND} values of all subjects in both ligands [^{11}C] NNC112 and [^{11}C]SCH23390. Filled circles represent controls and open circles represent patients. A. BP_{ND} measured by [^{11}C] NNC112; B. BP_{ND} measured by [^{11}C]SCH23390. The horizontal line represents the group mean. In all ROIs, statistically significant differences were observed between patients with schizophrenia and healthy controls (one-way ANCOVA with age as covariate, $p < 0.0125 = 0.05/4$).

Table 3
[^{11}C] NNC112 and [^{11}C]SCH23390 binding potential.

Region	[^{11}C]NNC112				[^{11}C]SCH23390			
	Controls ($n=12$)	Patients ($n=6$)	p value	Reduction (%)	Controls ($n=12$)	Patients ($n=6$)	p value	Reduction (%)
Frontal cortex	0.57 ± 0.064	0.39 ± 0.065	<0.001*	31.2	0.39 ± 0.043	0.28 ± 0.037	<0.001*	26.7
Anterior cingulate	0.75 ± 0.12	0.54 ± 0.14	0.009*	27.2	0.53 ± 0.083	0.40 ± 0.079	0.009*	23.5
Temporal cortex	0.61 ± 0.074	0.44 ± 0.037	<0.001*	27.7	0.40 ± 0.048	0.28 ± 0.038	<0.001*	29.9
Striatum	2.85 ± 0.31	2.25 ± 0.23	<0.001*	21.4	1.83 ± 0.18	1.45 ± 0.15	<0.001*	20.9

Data are mean ± SD.
* $p<0.0125$ (=0.05/4, Bonferroni corrected) ANCOVA with age as covariate ($df=1,15$).

HT_{2A} receptor (Slifstein et al. 2007). However, Okubo et al. (2000) reported no difference in binding in the prefrontal cortex using [^{11}C]N-methylspiperone as ligand for 5-HT2 receptor in the same schizophrenia patients who showed lower binding with [^{11}C]SCH23390 (Okubo et al. 1997) and a non-significant trend towards decreased binding. In this study, all patients were medicated with only sulpiride as antipsychotic drug. Sulpiride is a selective dopamine D_2 antagonist and has negligible affinity to dopamine D_1 receptor in vivo (Farde et al. 1989). All antipsychotics of the patients were changed to sulpiride. Even though sulpiride had no direct affinity to dopamine D_1 receptor, these patients had been receiving long-term chronic antipsychotic treatment. Several studies of primates have reported that chronic administration of dopamine D_2 receptor antagonist decreased the density of dopamine D_1 receptor (Lidow and Goldman-Rakic 1994; Lidow et al. 1997), although one animal study has reported that there was no influence of chronic medication on dopamine D_1 receptor density (Sanci et al. 2002). Hirvonen et al. (2006) reported a widespread reduction of D_1 receptor binding in the brain in patients with schizophrenia, which was associated with antipsychotic medication dose. However, we did not find a correlation between them, possibly due to a lack of variance in antipsychotic dose.

The patients in this study were in a very severe residual phase according to the deficits in the cognitive test scores (Table 2) and the high total scores of PANSS despite the low positive symptom scores (Table 1). Some studies have reported regional structural brain abnormalities of gray matter in the striatum and extrastriatal regions of schizophrenia patients with chronic antipsychotic treatment (Jernigan et al. 1991; Tamagaki et al. 2005). In this study, since we confirmed that there was no significant difference between the volume of each ROI in patients and that of controls, we measured the gray matter volume ratio in each ROI. The results revealed no significant difference between the gray matter volume in patients and that of controls in each ROI (data not shown). The values of reduction in BP_{ND} shown by percentage (Table 3) seemed considerably larger than the reduction of gray matter. However, the effect of brain gray matter reduction cannot also be ruled out.

Our results indicated lower dopamine D_1 receptor binding in schizophrenia patients with chronic antipsychotic treatment measured by different radioligands, [^{11}C]NNC112 and [^{11}C]SCH23390. However, as the small sample size was a distinct limitation of this study, a larger study population will be necessary to more definitively examine the relation between dopamine D_1 receptor binding and factors such as duration of illness and severity of symptoms.

Conflict of interest statement

There are no conflicts of interests.

Acknowledgements

This study was supported by a consignment expense for the Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government. The sponsors of the study had no role in the study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

We thank Mr. Takahiro Shiraishi and Mr. Akira Ando for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Ms. Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator, and Miho Shidahara is acknowledged for her valuable comments.

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Neuroscience Research 63 (2009) 115–121

Contents lists available at ScienceDirect

Neuroscience Research

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

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ARTICLE INFO

Article history:
Received 14 July 2008
Received in revised form 14 October 2008
Accepted 6 November 2008
Available online 14 November 2008

Keywords:
Time estimation
Interval timing clock
Cognitive science
Sleep
Circadian phase
Insomnia

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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doi:10.1016/j.neures.2008.11.001

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,

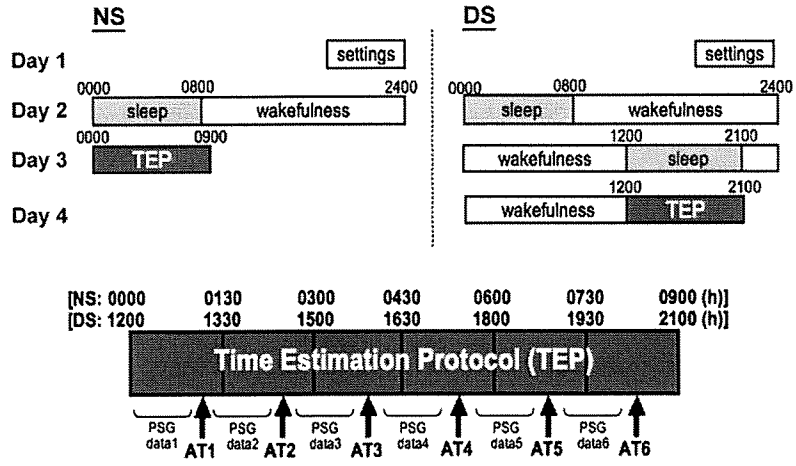

Fig. 1. Time estimation protocol (TEP). TEP was conducted between 00:00 h and 09:00 h (nighttime sleep: NS) or 12:00 h and 21:00 h (daytime sleep: DS). The 9-h polysomnography (PSG) recording periods were divided into six 90-min periods. We woke the participants and conducted a structured interview once 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

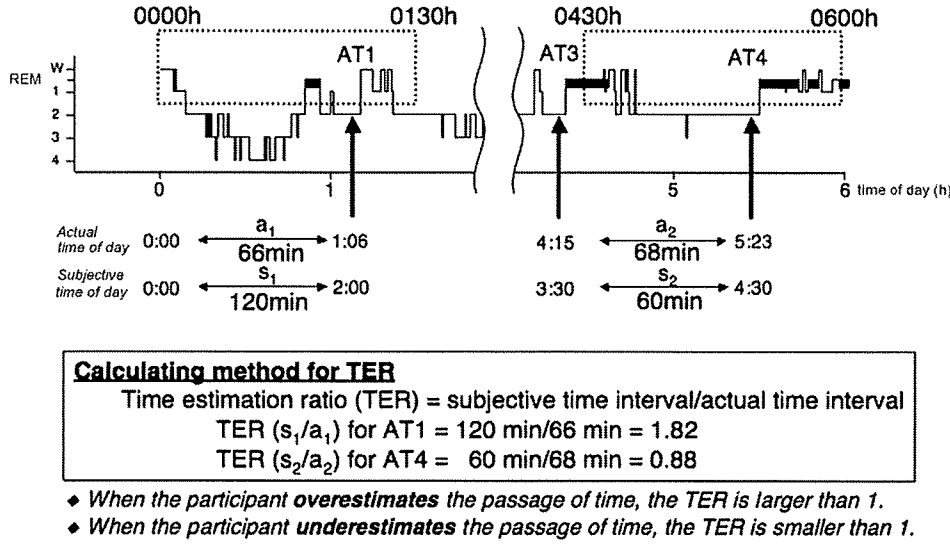

Fig. 2. Time estimation ratio (TER). Subjective time interval in both experiments was defined as the time difference between subjective times of the day, which were obtained at successive awakening trials (ATs). The actual time interval was defined as the actual time difference between successive ATs. 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

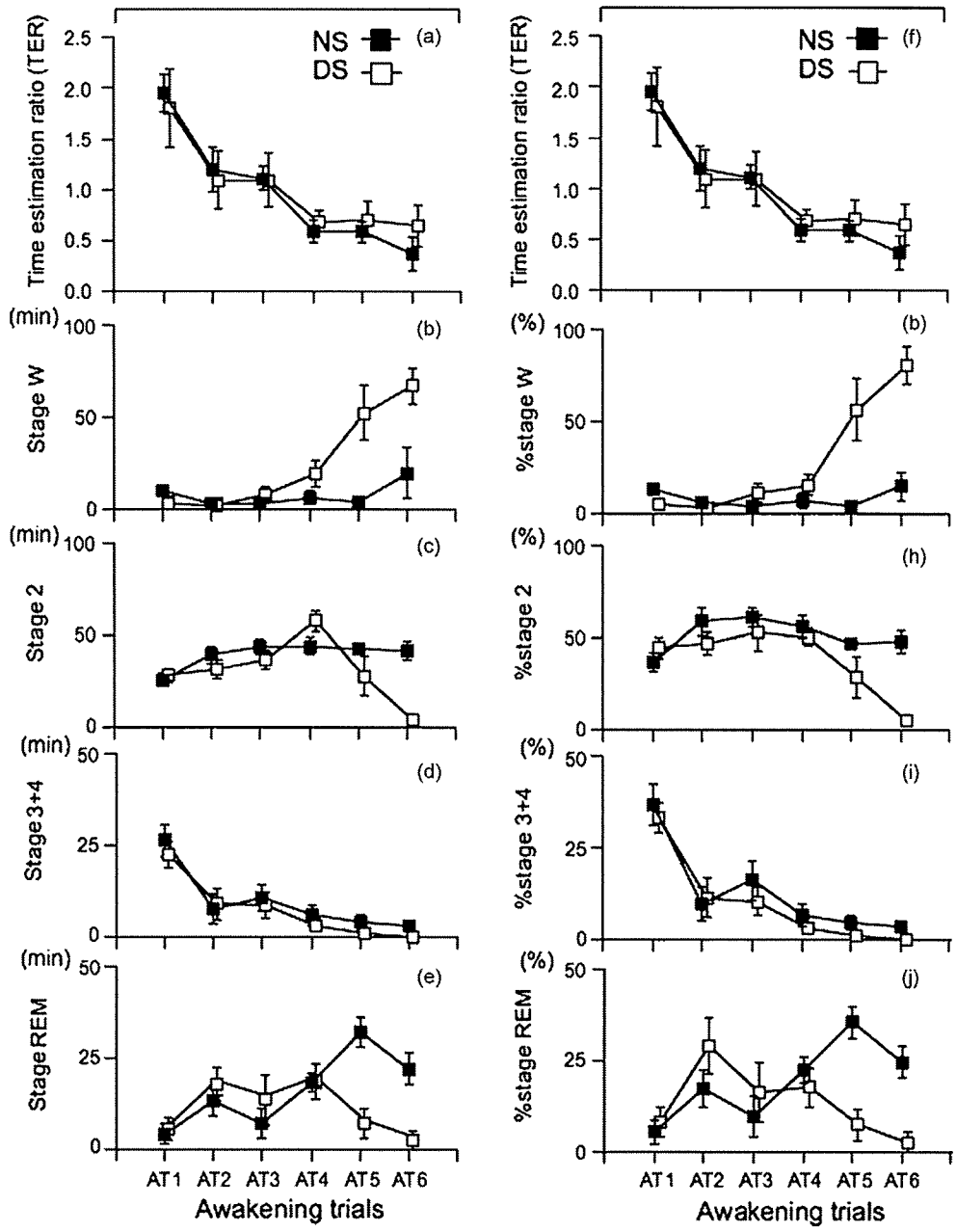

Fig. 3. (a–j) Time course of the mean time estimation ratio (TER) and the amounts (left panel) and the percentages (right panel) of sleep stages. Filled and open circles represent the data in nighttime sleep (NS) and daytime sleep (DS) experiments, respectively. The horizontal axes indicate the AT number. 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.

Acknowledgements

This study was supported in part by a Research Grant for Nervous and Mental Disorders (11-3) and a Health Science Grant (15130301) from the Ministry of Health, Labor and Welfare of Japan, and a Grant-in-aid for Scientific Research (13470200) from the Ministry of Education, Science and Culture of Japan.

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Sleep-related problems and use of hypnotics in inpatients of acute hospital wards

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Received 6 November 2009; accepted 26 January 2010

Abstract

Objective: Although sleep disorders are highly prevalent among patients with physical disorders, only limited information is available about the actual status of sleep-related problems in inpatients of acute hospital wards. We conducted a multicenter cross-sectional observational survey investigating the prevalence of sleep disorders and use of hypnotic-sedative drugs among inpatients of acute wards in 44 general hospitals in Japan.

Method: Questionnaire-, actigraph- and observation-based sleep evaluations were simultaneously performed in 557 adult inpatients [mean age 72.8±12.8 (S.D.) years] of acute wards during a one-month period in July 2007.

Results: Of the 421 patients with data available, 22.3% had at least one of the following sleep disorders: sleep apnea syndrome, restless legs syndrome, periodic limb movement disorder and nocturnal behavior disorder. Similarly, 62.7% had insomnia, 6.9% had severe daytime sleepiness and 12.8% had other sleep-related symptoms. Only 13.8% were free of any sleep-related problem. Although 33.7% of insomnia patients were taking hypnotic-sedative drugs, 65.2% of them complained of residual insomnia symptoms.

Conclusion: The findings obtained in this study have revealed the remarkably high prevalence of sleep-related problems experienced by inpatients of acute hospital wards in Japan. Proper diagnosis of sleep disorders should be made among patients with physical disorders.

Keywords: Sleep disorders; Insomnia; Acute hospital wards; Physical illness; Hypnotic use

1. Introduction

Sleep disorders, including insomnia, sleep apnea syndrome (SAS), restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), are highly prevalent and particularly common in elderly patients with physical disorders. Sleep disorders reduce patients' quality of life (QOL) by causing symptoms such as daytime sleepiness and cognitive impairment and may also exacerbate underlying disorders by inhibiting respiratory, cardiovascular and

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0163-8343/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.genhosppsych.2010.01.015

metabolic functions. In one study of older patients in a skilled-care geriatric hospital in Japan, the presence of insomnia was associated with a higher risk of mortality during the 2-year follow-up period [1].

The prevalence of these sleep disorders increases with age [2], and the high incidence of physical disorders among the elderly population is a contributing factor. Previous epidemiologic studies have revealed that the prevalence of insomnia among the general population is 10.2–48.0% [3–6], and insomnia frequently occurs in association with chronic pain disorders, respiratory diseases and neurological diseases [7]. SAS, RLS or PLMD also frequently coexists with various physical diseases including hypertension [8], ischemic heart disease [9,10], chronic kidney failure [11], iron-deficiency anemia [12] and neurological diseases such as Parkinson's disease [13]. It is also noteworthy that medications used for the treatment of sleep disorders may worsen physical disorders; for example, most standard hypnotics benzodiazepines cause *sleep apnea* by reducing the muscle tone of the upper respiratory tract during sleep [14].

The fact that physical and sleep disorders can coexist at a high frequency should always be taken into account when making an accurate diagnosis and developing a treatment strategy that provides a favorable risk-benefit balance. Nevertheless, we currently have only limited information about the actual status of sleep-related problems experienced by inpatients of acute hospital wards. Thus, the objectives of the present study were to investigate the breakdown and prevalence of sleep disorders and use of hypnotic-sedative drugs in acute ward inpatients and to identify problems in the clinical practice of sleep medicine.

2. Methods

2.1. Subjects and method

Study subjects who were 20 years of age or more were randomly selected from among the inpatients of acute hospital wards, excluding psychiatric and tuberculosis wards, of 44 general hospitals in Japan. The patients' identities were coded at each hospital ward, and then patients were randomly sampled. The investigation was carried out among 557 subjects [316 males, 241 females; mean age, 72.8±12.8 (S.D.) years; range 22–96 years] who had provided informed consent or whose family member had provided informed consent, simultaneously at all hospitals during a period of 1 month in July 2007. Each patient's primary disorder was classified according to the International Classification of Diseases and Related Health Problems Version 10 (*ICD-10*) (Table 1). The ethics committee at each research site approved the present study.

2.2. Investigation methods

The investigation was conducted over 2 days for each patient to check his or her sleep condition and details of treatment. The investigation consisted of subjective sleep evaluation using a self-administered questionnaire (Table 2), objective sleep evaluation by actigraphy, observational sleep evaluation by nursing staff and a survey of medication use as recorded in the medical records.

The questionnaire was designed to identify the presence of insomnia, SAS, RLS, PLMD, nocturnal behavior disorder (NBD), daytime sleepiness and nocturnal sleep-related symptoms. In the questionnaire, Q1–Q6 were completed by the patients, and Q7 and Q8 were completed by medical staff. Although NBD can be further divided into nocturnal delirium, REM sleep behavior disorder, behavioral and psychological symptoms of dementia and other symptoms, these disorders were not distinguished in view of the primary objective of the present study and technical restrictions.

For objective sleep evaluation, subjects were asked to wear an actigraph [Lifecorder PLUS (LC), Suzuken, Nagoya, Japan] [15] on their waist for two consecutive days for continuous recording of the intensity of activity. Total sleep time (TST; the sum of all sleep time during time in bed), total wake time (TWT; the sum of all wake time during time in bed) and sleep efficiency (SE; the percentage of TST relative to time in bed) were then calculated from the LC data. Time in bed (TIB) was defined as the time during

Table 1
Illness identified in enrolled patients

System organ/disease class	Total	SAS, RLS, PLMD and NBD	Insomnia			Good Sleep
	557 (100%)	94 (100%)	Improved 31 (100%)	Untreated 175 (100%)	Not-Improved 58 (100%)	63 (100%)
Diseases of the circulatory system	140 (25.1)	20 (21.3)	7 (22.6)	44 (25.1)	9 (15.5)	15 (23.8)
Neoplasms	127 (22.8)	19 (20.2)	5 (16.1)	47 (26.9)	26 (44.8)	8 (12.7)
Diseases of the respiratory system	68 (12.2)	11 (11.7)	3 (9.7)	17 (9.7)	8 (13.8)	9 (14.3)
Diseases of the digestive system	62 (11.1)	13 (13.8)	2 (6.5)	21 (12.0)	7 (12.1)	8 (12.7)
Diseases of the nervous system	45 (8.1)	11 (11.7)	2 (6.5)	9 (5.1)	3 (5.2)	5 (7.9)
Diseases of the genitourinary system	16 (2.9)	4 (4.3)	1 (3.2)	5 (2.9)	1 (1.7)	3 (4.9)
Diseases of the musculoskeletal system and connective tissue	14 (2.5)	2 (2.1)	1 (3.2)	7 (4.0)	0 (0.0)	3 (4.9)
Certain infectious and parasitic diseases	8 (1.4)	0 (0.0)	1 (3.2)	3 (1.7)	1 (1.7)	0 (0.0)
Other diseases	77 (13.8)	14 (14.9)	9 (29.0)	22 (12.6)	3 (5.2)	12 (19.0)

SAS; sleep apnea syndrome, RLS; restless legs syndrome, PLMD; periodic limb movement disorder, NBD; nocturnal behavior disorder.

Table 2
Question items and percentages of respondents in the analyzed 421 inpatients

Items		1)	2)	3)	4)
Q1. How long did it take from light off until you went to sleep? 1) less than 15 minutes 2) 15-29 minutes 3) 30-59 minutes 4) more than 60 minutes		50.4	20.4	14.5	14.7
Q2. How many times did you awake during last night? 1) none 2) 1-2 times 3) 3-4 times 4) more than 5 times		21.4	35.9	24.9	17.8
Q3. What time did you get up this morning (h:min)?		22.6*	77.4		
Q4. Did you get up in the morning unrefreshed or nonrestored? 1) good 2) fair 3) insufficient 4) poor		38.7	37.1	19.2	5.0
Q5. Do you have daytime sleepiness?** 1) none 2)some 3) moderate 4) severe		22.8	22.8	47.5	6.9
Q6. Did you experience any of the following symptoms during last night (completed by a patient)					
Q6-a creeping sensation or restless discomfort in the limbs	1) yes 2) no	5.9	94.1		
Q6-b legs or arms jerk	1) yes 2) no	2.4	97.6		
Q6-c hot flash	1) yes 2) no	4.8	95.2		
Q6-d night sweat	1) yes 2) no	6.9	93.1		
Q6-e palpitation	1) yes 2) no	1.2	98.8		
Q6-f anxiety or panic	1) yes 2) no	1.0	99.0		
Q6-g sleep paralysis	1) yes 2) no	0.0	100.0		
Q6-h nightmare	1) yes 2) no	3.1	96.9		
Q7. Did the patient experience any of the following symptoms during last night (completed by nursing staffs)					
Q7-a loud snoring, or apnea lasting for 10 seconds or longer	1) yes 2) no	10.0	90.0		
Q7-b periodic legs or arms jerk	1) yes 2) no	2.1	97.9		
Q7-c sleep-talking, delirium or abnormal behaviors such as wandering	1) yes 2) no	6.9	93.1		
Q8. Whether or not the patient took any hypnotic-sedative drug(s) for treatment of insomnia within the past one week and the name of the drug(s) if any (completed by nursing staffs) 1) yes 2) no Name of drugs [ ]		27.6	72.4		

* Patients who woke up 30 minutes or earlier than the desired time without falling asleep again (Q3).
** answered at 2 pm.

which patients were supposed to be in bed as specified by each hospital ward, and specifically the time from "lights out" to the time at which patients were expected to wake. Mean TIB was approximately between 9 p.m. and 6 a.m. Observations by the nursing staffs on each of the wards confirmed that the patients were in bed during TIB on the evenings of the study.

For the observational sleep evaluations, several nursing staffs alternated in order to record continuously the subjects' sleep states. Opening and closing of eyes, breathing, movement and any unusual behavior of the subjects were observed and recorded at a distance so as to not disturb the subjects.

2.3. Differential diagnosis of sleep disorders

The diagnostic flow for the patients included in the investigation is shown in Fig. 1. Some of the preselected subjects (n=136) were either excluded from data analyses or could not participate due to reasons such as sudden change in physical condition such as fever, severe dementia, consciousness disturbance due to organic brain damages, need for emergency examination, hospital transfer or discharge or due to missing data on their amount of physical activity. As a result, a total of 421 patients comprised the analysis population [228 males, 193 females; mean age, 72.5±12.6 (S.D.) years; range 22-96 years]. The number of respondents for each question item is shown in Table 2.

Patients were initially examined for the presence of SAS (positive answer to Q7-a), RLS (positive answer to Q6-a), PLMD (positive answer to Q6-b or Q7-b) or NBD (positive answer to Q7-c). Those who were NOT diagnosed with SAS, RLS, PLMD or NBD were subsequently examined for the presence of insomnia. Patients were judged as having insomnia when the subjective sleep investigation indicated the presence of any one of the following:

i. Disturbances of initiating sleep (DIS): Q1, the answer indicates 30 min or more.
ii. Disturbances of maintaining sleep (DMS): Q2, the answer indicates three times or more.
iii. Early morning awakening (EMA): Q3, the answer indicates wake time 30 minutes or earlier than the desired time without falling asleep again.
iv. Non-restorative sleep (NRS): Q4, the answer indicates insufficient or poor sleep.

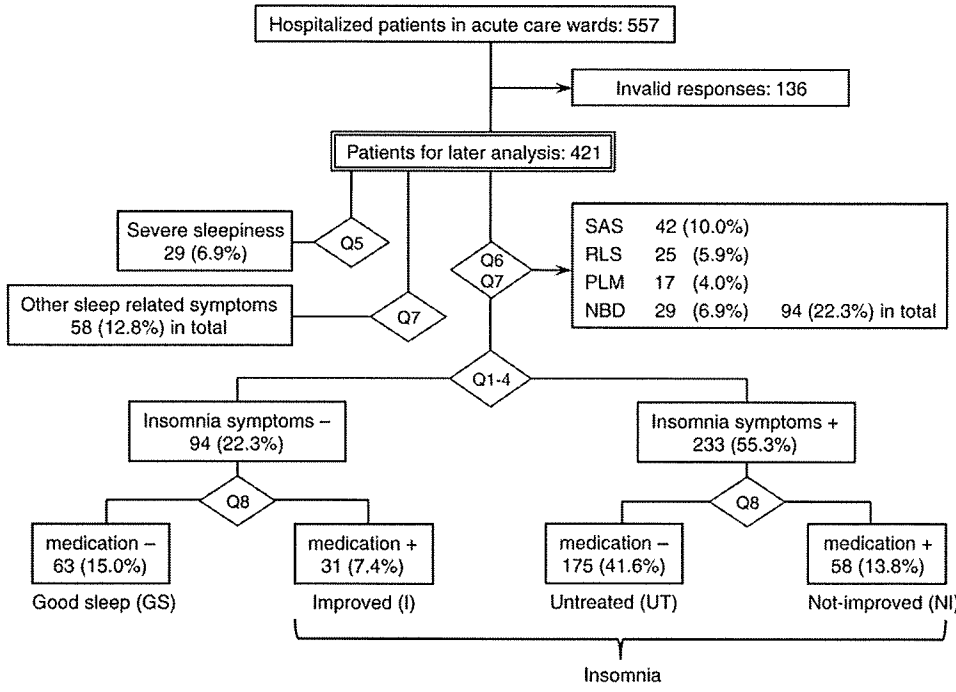

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

The subjects were also divided into the following four groups according to the presence or absence of insomnia and use or not of hypnotic-sedative drugs for insomnia treatment: the good sleep (GS) group consisting of those without insomnia and taking no medication, the improved (I) group consisting of those without insomnia and taking medication (s), the untreated (UT) group consisting of those with insomnia but taking no medication, and the not-improved (NI) group consisting of those with insomnia and taking medication(s). Of these groups, the I, UT and NI groups were grouped together and defined as the insomnia group (Fig. 1).

2.4. Daytime sleepiness

The 421 patients were examined for the presence or absence of daytime sleepiness according to the following criteria: Q5, the answer indicates the presence of moderate or severe sleepiness.

2.5. Sleep-related symptoms

The 421 patients were examined for the presence or absence of other sleep-related symptoms, such as hot flashes in the foot or body (Q6-c), night sweats (Q6-d), palpitations (Q6-e), anxiety and panic (Q6-f), sleep paralysis (Q6-g) and nightmares (Q6-h).

2.6. Statistical analysis

One-way analysis of variance followed by Tukey's multiple comparison tests was used to identify significant differences in sleep parameters (TST, TWT and SE) among the insomnia group and GS group. Sleep parameters were also compared between each sleep disorder group and the GS group using a two-tailed Student's t test. Analysis values are expressed as mean±S.D. Multiple logistic regression analysis was carried out to calculate the odds ratio (OR) and 95% confidence interval (CI) for assessing the association of primary disorders, sleep disorders and use of hypnotic-sedative drugs with severe sleepiness. Presence of severe sleepiness was used as the dependent variable, and primary disorders, sleep disorders and use of hypnotic-sedative drugs were used as independent variables. We performed multiple logistic regression analyses to control for all sociodemographic (sex and age) and other factors. Statistical significance was set at $P<.05$. All analyses were made using SPSS 11.5 for Windows.

3. Results

3.1. Prevalence of sleep disorders

The breakdown of the diagnoses of sleep disorders is shown in Fig. 1. Of the 421 inpatients, 42 (10.0%, M/F=29/13) had SAS, 25 (5.9%, 14/11) had RLS, 17 (4.0%, 11/6) had PLMD and 29 (6.9%, 19/10) had NBD. A total of 94 (22.3%) had at least one of the four sleep disorders. Seventeen patients had two sleep disorders concurrently.

Of the 421 inpatients, 58 (13.8%, NI) and 175 (41.6%, UT) complained of insomnia symptoms. A total of 264 (62.7%), including the NI, UT and I (31, 7.4%) groups were given a diagnosis of insomnia. The most common insomnia

Table 3
Comparison of objective sleep parameters determined by LC in the insomnia and good sleep patients

	SAS n=42	P	RLS n=25	P	PLMD n=17	P	NBD n=29	P	Insomnia						Good sleep n=63
									Untreated n=175	P	Improved n=31	P	Not-improved n=58	P	
TST (min)	367.6±119.2	.06	331.9±117.7	0	354.6±111.5	.01	359.8±126.1	.04	369.2±102.5	.04	400.7±118.4	n.s	399.7±91.0	n.s	409.4±102.4
TWT (min)	172.4±119.2	.05	208.1±117.7	0	185.4±111.5	.01	180.2±126.1	.04	170.3±102.3	.03	139.4±118.4	n.s	140.3±91.0	n.s	129.3±103.3
SE (%)	68.1±22.1	.05	61.5±21.8	0	65.7±20.6	.01	66.6±23.4	.04	68.4±19.0	.03	74.2±21.9	n.s	74.0±16.9	n.s	76.1±19.1

Value are expressed as mean±S.D..
P value vs. Good sleep group.
n.s; not significant.

symptom was DMS (60.1%), followed by DIS (41.2%), EMA (33.9%) and NRS (31.8%). Only 63 (15.0%) were free of the above-mentioned sleep disorders and were assigned to the GS group.

3.2. Objective sleep parameters

Sleep parameters in each sleep disorder group are summarized in Table 3. There were significant differences in TST [F(3,323)=3.24, P=.022], TWT [F(3,323)=3.28, P=.021] and SE [F(3,323)=3.31, P=.020) among the insomnia group and GS group. TST (P=.039) was significantly shorter and TWT (P=.033) and SE (P=.032) were significantly longer in the NI group than in the GS group. Patients with RLS (P<.01) and NBD (P<.05) also presented a significantly shorter TST, significantly longer TWT and significantly lower SE than those in the GS group. A similar tendency was observed for patients with SAS or PLMD (P<.06). On the other hand, we found no significant differences in the sleep parameters between the medicated group (the I or NI group) and the GS group, regardless of whether or not any subjective improvement was observed.

3.3. Daytime sleepiness

Of the 421 inpatients, 229 (54.4%) experienced moderate to severe sleepiness and 29 (6.9%) experienced severe sleepiness. Severe sleepiness was commonly observed in those with sleep disorders; it was most commonly observed in patients with multiple sleep disorders (27.8%, 5/18), followed by those with PLMD (18.2%, 2/11), SAS (17.9%, 5/28) and NBD (17.7%, 3/17). Multiple logistic regression analysis revealed that SAS (adjusted OR=3.78, 95% CI, 1.24–11.53, P<.05) and PLMD (adjusted OR=5.93, 95% CI, 1.50–23.4, P<.05) showed a significantly positive association with the presence of severe sleepiness.

3.4. Other sleep-related symptoms

Of the 421 inpatients, 19 (4.5%, M/F=7/12) had hot flashes, 29 (6.9%, 13/16) had night sweats, 5 (1.2%, 1/4) had palpitations, 4 (1.0%, 2/2) had anxiety or panic and 13 (3.1%, 7/6) had nightmares. None of the patients experienced sleep paralysis.

3.5. Prevalence of use of hypnotic-sedative drugs

Of the 421 inpatients, 116 (27.6%) were taking some kind of hypnotic-sedative drug for the treatment of insomnia symptoms. The breakdown of the prescribed drugs was as follows: benzodiazepine hypnotics including zolpidem and zopiclone accounted for 73.2% (26.1% for ultrashort-acting, 30.6% for short-acting and 16.5% for intermediate-acting), benzodiazepine anxiolytic accounted for 5.8%, antipsychotics accounted for 15.6% and other drugs accounted for 5.2% of all prescribed drugs. In the insomnia group, those receiving medication therapy for insomnia only accounted for 33.7% (the I+NI group). Two thirds of the patients receiving medication therapy (65.2%, corresponding to the NI group) complained of persistent insomnia symptoms. In addition, 36.0% of RLS patients, 29.4% of PLMD patients, 26.2% of SAS patients and 17.2% of NBD patients were taking at least one of the above hypnotic-sedative drugs.

4. Discussion

This is the first multicenter study investigating the prevalence of sleep disorders in inpatients of acute wards in general hospitals. Sleep disorders are extremely common disorders among community residents, and are even more so among patients with underlying physical diseases as in the subjects of the present study. Insomnia, as well as other sleep disorders, while frequently thought to be transitory or secondary to a physical disease, can become prolonged without appropriate treatment in the early stages. Furthermore, chronic sleep disorders can exacerbate lifestyle-related diseases such as hypertension and diabetes, and increase the risk of psychiatric symptoms such as depression and anxiety, not to cause subjective distress [16,17]. Many sleep disorders go undetected and are not appropriately treated in clinical practice. Therefore, this study was conducted to alert practitioners of sleep disorders to this situation, by shedding more light on their current status in general medical practice.

In the present study, we investigated the prevalence of sleep disorders and the use of hypnotic-sedative drugs in 421 inpatients with mean age of 72.5 years by questionnaire-, actigraph- and observation-based sleep evaluations, and have revealed a high prevalence of diverse types of sleep disorders

in the study population. SAS, RLS, PLMD, NBD and insomnia, in particular, were highly prevalent (10.0, 5.9, 4.0, 6.9 and 62.7%, respectively). The inpatients also suffered from various sleep-related symptoms (1.0–6.9%, except for sleep paralysis), which are common conditions with physical disorders and which could cause disrupted sleep [18–21]. In fact, the patients with these sleep disorders also showed poor sleep parameters recorded by actigraphy, which objectively indicates that they have poor-quality sleep during the night. Consequently, of the 421 patients, only 13.8% were free of any type of sleep disorder diagnosed, severe daytime sleepiness or sleep-related symptoms, revealing that sleep-related problems are very common clinical problems among inpatients of acute hospital wards.

Due to restrictions on the disclosure of personal information, the only information available regarding the underlying diseases of the patients was the names of the primary diseases according to the major classification of the *ICD-10*. We were thus unable to analyze respective medical conditions that are commonly associated with these sleep disorders, such as chronic pain, cardiovascular diseases, chronic renal failure, hemodialysis and iron deficiency anemia.

The prevalence of SAS and RLS is generally high in elderly people and patients with physical disorders. However, even though the mean age of our patients was high (72.5 years) and they had physical disorders in the exacerbation phase, contrary to our expectations, the prevalence of SAS and RLS was not higher in the study population than in community dwellers of previous studies. For example, the prevalence of SAS in middle-aged to elderly people has been shown to be 9–10% in males and 4–10% in females [22,23], which is comparable to that in the present study population (10% in the entire population, 12.7% in males, 6.7% in females). In the present study, patients were defined as having SAS if they reported loud snoring or apnea lasting for 10 seconds or more, because loud snoring is the most prominent symptom of upper airway resistance syndrome, which is included in the category of SAS [7,24]. Nevertheless, the prevalence of SAS patients including those who snored loudly in the present study was similar to that in the general population. Similarly, a large-scale survey which employed a self-administered questionnaire and used a definition of RLS similar to that in the present study has reported that the prevalence of RLS among Japanese people aged 70 years or more is 4.1% (3.4% in males, 4.6% in females), which is practically identical to that in the present study (5.9% in total, 6.1% in males, 5.7% in females) [25]. Furthermore, the frequency of NBD was as low as 6.9%, despite the occurrence rate of delirium per admission varying between 11 and 42% [26]. The low NBD frequency of the present study compared to that of all previous studies is thought to be because patients with severe physical conditions or with organic brain damages were excluded from the analyses.

In many of the epidemiologic studies on the prevalence of sleep disorders, sleep evaluation is performed during a period of one week to one month. The fact that sleep evaluation in this study was performed on a single night might have held down the prevalence of sleep disorders. However, since the physical status of the inpatients of acute hospital wards can change in a very short period of time and their sleep condition is also subject to change, we assumed that the results obtained from a long investigation period would not properly reflect the actual status of their sleep-related problems. Extension of the duration for determining the presence or absence of sleep disorders may result in a dramatic increase in the prevalence of the sleep disorders in inpatients of acute hospital wards.

Patients with physical disorders, especially with advanced age, are generally vulnerable to insomnia [27–29]. We have found that approximately two thirds (62.7%) of the representative patients in acute wards in Japan are suffering from insomnia. It was confirmed not only from the subjective complaints of patients but also from the objective sleep evaluation that the quality of sleep for patients with insomnia receiving no treatment or who had other sleep disorders was significantly lower than that for patients in the GS group (Table 3). A survey among 1500 community dwellers aged 55–84 years in the United States has demonstrated that the quality of sleep decreases in proportion to an increase in the number of physical disorders suffered [27]. Several studies have also reported a high prevalence (34–69%) of insomnia in outpatients of primary care clinics or regular inpatients with acute or chronic physical disorders [30–33]. The findings of the present study for acute ward inpatients are consistent with those obtained in the previous studies in spite of shorter-term sleep evaluation.

In many cases of sleep disorders, daytime sleepiness often occurs to compensate for low-quality sleep during the night. In the present study, 47.5% of the patients experienced mild or severer sleepiness and 6.9% experienced severe sleepiness, which was particularly high in those with multiple sleep disorders, including SAS, RLS, PLMD and NBD. The results of multiple logistic regression analysis indicated that severe sleepiness is significantly associated with SAS and PLMD, and not with an underlying disease or type of hypnotic-sedative drug.

Only one-third (33.7%) of the patients with insomnia included in the present investigation received treatment for insomnia symptoms. In addition, two-thirds (65.2%) of the patients receiving medication therapy complained of residual insomnia symptoms. The relatively low frequency of patients prescribed hypnotic-sedative drugs in the present study, which is very similar to that reported in the Meissner's study [30], suggests the possibility that physicians are not fully aware of the presence of insomnia in their patients.

The prescribed drugs mainly consisted of benzodiazepine hypnotics including intermediate-acting agents and antipsychotics. Caution should always be exercised when

using these hypnotic-sedative drugs in inpatients with physical disorders, especially in elderly patients. This is because elderly patients present a poor risk-benefit balance for hypnotic-sedative drugs due to such reasons as decreased drug metabolizing capacity, increased drug sensitivity, risk of fall and fracture or suppressed mental function, and worsening of underlying diseases induced by medication [34–37].

Moreover, administered hypnotic-sedative drugs may be ineffective or even worsen underlying diseases unless sleep disorders are properly diagnosed. In fact, 23.8% of the patients with SAS were prescribed hypnotic-sedative drugs including benzodiazepines and 36.0% of the patients with RLS were taking hypnotic-sedative drugs other than clonazepam. These results suggest that medications that are not necessarily appropriate for treatment of individual patients' sleep disorders are often selected in actual clinical practice, possibly causing a reduction in the patients' ADL and QOL.

Several limitations should be noted when interpreting the results of the present study. First, as elderly patients aged 65 years or more accounted for a large portion (76.0%) of the 421 inpatients, it is speculated that the high prevalence of sleep-related problems observed in the patients of the present investigation were associated with not only sleep disorders attributable to physical disorders but also age-related changes in sleep property.

Second, one-fourth (24.4%) of the initially enrolled 557 patients were excluded. Patients who were unable to answer questions on the day of the survey because of a change in their physical condition (e.g. fever, consciousness disturbance or need for emergency examination) or those patients with missing data due to interruptions in LC data collection were excluded. Some of these excluded patients might have developed some type of sleep disorder during their stay in hospital.

Third, insomnia defined in the present study is different from insomnia that meets the general criteria of the International Classification of Sleep Disorders, second edition (ICSD-2) [7], because we did not consider the presence or absence of "daytime impairment related to the nighttime sleep difficulty". This investigation item was not included in the present study because it was difficult to determine whether the patients' diverse psychosomatic symptoms observed during the daytime were attributable to insomnia or physical disorders.

Fourth, the questionnaire employed in the present study has not been validated. A set number of items taken from the original were configured so as to reduce the burden on inpatients who were in poor physical condition. Therefore, the questionnaire can only suggest the possibility of certain disorders such as SAS, PLMD and RLS; it does not predict the presence of these disorders with high accuracy. However, the frequency of sleep disorders and the percentage of patients exhibiting symptoms of insomnia found in the present study closely resemble the data of several other studies. This is thought to be indirect evidence that, to a certain degree, the survey items work effectively to detect patients suffering from sleep disorders.

Fifth, the sleep/wake scoring algorithm used for the LC data in the present study has been validated for a sample of healthy young subjects [15], but not for elderly subjects with physical disorders, as in the present study's sample. However, as the results demonstrate, meaningful differences were detected in the sleep parameters calculated with this algorithm for total sleep time, total wake time, and efficiency of sleep between the UT group with insomnia and the GS group. Given this, the clinical application of the LC and sleep/wake scoring algorithm for the subjects of the present study can be considered a sound approach to a certain degree.

5. Conclusion

In the present study, which initially involved 557 inpatients who had been admitted to acute hospital wards in 44 general hospitals, we have revealed an extremely high prevalence of sleep disorders using subjective and objective sleep evaluation scales, and have also indicated several problems in the current practice of sleep medicine. Proper diagnosis of sleep disorders should be made while being aware of the high prevalence of sleep disorders among elderly patients with physical disorders, and a treatment strategy that provides a favorable risk-benefit balance must be developed.

Acknowledgments

This study was supported by a Grant-in-Aid for Cooperative Research from the Ministry of Health, Labor, and Welfare of Japan (H19-kokoro-ippan-013, H20-tyojyu-ippan-001).

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Psychiatry and Clinical Neurosciences 2009; 63: 209–217 doi:10.1111/j.1440-1819.2009.01941.x

Regular Article

Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: A study with fMRI

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Aims: Antisaccadic eye movements, requiring inhibition of a saccade toward a briefly appearing peripheral target, are known to be impaired in schizophrenia. Previous neuroimaging studies have indicated that patients with schizophrenia show diminished activations in the frontal cortex and basal ganglia. These studies used target fixation as a baseline condition. However, if the levels of brain activities at baseline are not compatible between patients and healthy subjects, between-group comparison on antisaccade-related activations is consequently invalidated. One possibility is that patients with schizophrenia may present with greater activation during fixation than healthy subjects. In order to examine this possibility, here we investigated brain activities associated with antisaccade in the two groups without using target fixation at baseline.

Methods: Functional brain images were acquired during prosaccades and antisaccades in 18 healthy subjects and 18 schizophrenia patients using a boxcar functional magnetic resonance imaging design. Eye movements were measured during scanning.

Results: In the patient group, the elevated activities in the dorsolateral prefrontal cortex (DLPFC) and thalamus, normally seen in antisaccade tasks relative to saccade tasks, were no longer observed. Moreover, in normal subjects, activities in the DLPFC and thalamus were greater during the antisaccade task than during the saccade task. In patients, no such difference was observed between the two tasks, suggesting that these brain regions are likely to be highly activated even by a simple task such as fixation. In particular, the DLPFC and thalamus in patients were not activated at a level commensurate with the difficulty of the tasks presented.

Conclusions: From these results, it is suggested that schizophrenia entails dysfunctions in the fronto-striato-thalamo-cortical network associated with motor function control.

Key words: antisaccade, fMRI, hyperfrontality, saccade, schizophrenia.

SACCADIC EYE MOVEMENTS are the primary mechanism used by primates to visually explore their environments. A visually guided reflexive saccade can be defined as an automatic orienting response to a novel visual target in the peripheral field. Patients with schizophrenia perform prosaccades normally, making rapid and accurate eye movements to targets.[1–3] In contrast, the inhibition of

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Received 18 August 2008; revised 26 November 2008; accepted 3 December 2008.