Jueptner, M., Rijntjes, M., Weiller, C., Faiss, J.H., Timmann, D., Mueller, S.P., Diener, H.C., 1995. Localization of a cerebellar timing process using PET. Neurology 45, 1540–1545.
Kaida, K., Nakano, E., Nittono, H., Hayashi, M., Hori, T., 2003. The effects of self-awakening on heart rate activity in a short afternoon nap. Clin. Neurophysiol. 114, 1896–1901.
Kajimura, N., Uchiyama, M., Takayama, Y., Uchida, S., Uema, T., Kato, M., Sekimoto, M., Watanabe, T., Nakajima, T., Horikoshi, S., Ogawa, K., Nishikawa, M., Hiroki, M., Kudo, Y., Matsuda, H., Okawa, M., Takahashi, K., 1999. Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. J. Neurosci. 19, 10065–10073.
Kleitman, N., 1963. Sleep and Wakefullness. Univ. Chicago Press, Chicago, pp. 122–126.
Kuriyama, K., Uchiyama, M., Suzuki, H., Tagaya, H., Ozaki, A., Aritake, S., Shibui, K., Xin, T., Lan, L., Kamei, Y., Takahashi, K., 2005. Diurnal fluctuation of time perception under 30-h sustained wakefulness. Neurosci. Res. 53, 123–128.
Lalonde, R., Hannequin, D., 1999. The neurobiological basis of time estimation and temporal order. Rev. Neurosci. 10, 151–173.
Lavie, P., Oksenberg, A., Zomer, J., 1979. It's time, you must wake up now. Percept. Mot. Skills 49, 447–450.
Lewis, P.A., Miall, R.C., 2003. Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. Curr. Opin. Neurobiol. 13, 250–255.
Lewis, S.A., 1969. Subjective estimates of sleep: an EEG evaluation. Br. J. Psychol. 60, 203–208.
Mangels, J.A., Ivry, R.B., Shimizu, N., 1998. Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. Brain Res. Cogn. Brain Res. 7, 15–39.
Maquet, P., Lejeune, H., Pouthas, V., Bonnet, M., Casini, L., Macar, F., Timsit-Berthier, M., Vidal, F., Ferrara, A., Degueldre, C., Quaglia, L., Delfiore, G., Luxen, A., Woods, R., Mazziotta, J.C., Comar, D., 1996. Brain activation induced by estimation of duration: a PET study. Neuroimage 3, 119–126.
Moiseeva, N.I., 1975. The characteristics of EEG activity and the subjective estimation of time during dreams of different structure. Electroencephalogr. Clin. Neurophysiol. 38, 569–577.
Moorcroft, W.H., Kayser, K.H., Griggs, A.J., 1997. Subjective and objective confirmation of the ability to self-awaken at a self-predetermined time without using external means. Sleep 20, 40–45.
Morell, V., 1996. Setting a biological stopwatch. Science 271, 905–906.
Perlis, M.L., Giles, D.E., Mendelson, W.B., Bootzin, R.R., Wyatt, J.K., 1997. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J. Sleep Res. 6, 179–188.
Pouthas, V., Maquet, P., Garnero, L., Ferrandez, A.M., Renault, B., 1999. Neural bases of time estimation: a PET and ERP study. Electroencephalogr. Clin. Neurophysiol. Suppl. 50, 598–603.
Rao, S.M., Harrington, D.L., Haaland, K.Y., Bobholz, J.A., Cox, R.W., Binder, J.R., 1997. Distributed neural systems underlying the timing of movements. J. Neurosci. 17, 5528–5535.
Rao, S.M., Mayer, A.R., Harrington, D.L., 2001. The evolution of brain activation during temporal processing. Nat. Neurosci. 4, 317–323.
Rechtschaffen, A., Kales, A., 1968. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Public Health Service, US Government, Printing Office, Washington DC.
Salin-Pascual, R.J., Roehrs, T.A., Merlotti, L.A., Zorick, F., Roth, T., 1992. Long-term study of the sleep of insomnia patients with sleep state misperception and other insomnia patients. Am. J. Psychiatry 149, 904–908.
Schubotz, R.I., Friederici, A.D., von Cramon, D.Y., 2000. Time perception and motor timing: a common cortical and subcortical basis revealed by fMRI. Neuroimage 11, 1–12.
Spencer, R.M., Zelaznik, H.N., Diedrichsen, J., Ivry, R.B., 2003. Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. Science 300, 1437–1439.
Tart, C.T., 1970. Waking from sleep at a preselected time. J. Am. Soc. Psychosom. Dent. Med. 17, 3–16.
Vanable, P.A., Aikens, J.E., Tadimeti, L., Caruana-Montaldo, B., Mendelson, W.B., 2000. Sleep latency and duration estimates among sleep disorder patients: variability as a function of sleep disorder diagnosis, sleep history, and psychological characteristics. Sleep 23, 71–79.
Weitzman, E.D., Czeisler, C.A., Zimmerman, J.C., Ronda, J.M., 1980. Timing of REM and stages 3 + 4 sleep during temporal isolation in man. Sleep 2, 391–407.
Zepelin, H., 1986. REM sleep and the timing of self-awakenings. Bull. Psychom. Soc. 24, 254–256.
Zung, W.W., Wilson, W.P., 1971. Time estimation during sleep. Biol. Psychiatry 3, 159–164.

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

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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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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 557 (100%)	SAS, RLS, PLMD and NBD 94 (100%)	Insomnia			Good Sleep 63 (100%)
			Improved 31 (100%)	Untreated 175 (100%)	Not-Improved 58 (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.

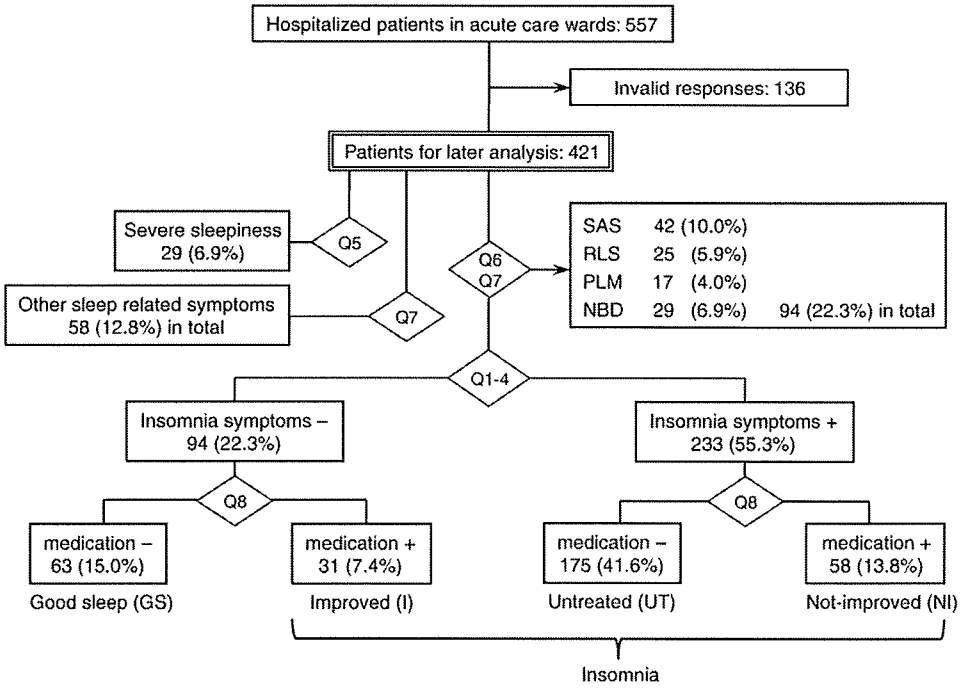

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

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.

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References

[1] Manabe K, Matsui T, Yamaya M, Sato-Nakagawa T, Okamura N, Arai H, et al. Sleep patterns and mortality among elderly patients in a geriatric hospital. Gerontology 2000;46:318–22.
[2] Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ 2007;176: 1299–304.
[3] Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257–62.
[4] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention. JAMA 1989; 262:1479–84.
[5] Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R. An epidemiological study of insomnia among the Japanese general population. Sleep 2000;23:41–7.
[6] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97–111.

[7] American Acdemy of SleepMedicine. International classification of sleep disorders :Diagnostic and coding manual. 2nd ed. Westchester: Illinois; 2005.
[8] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
[9] Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–9.
[10] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251–7.
[11] Hui DS, Wong TY, Li TS, Ko FW, Choy DK, Szeto CC, et al. Prevalence of sleep disturbances in Chinese patients with end stage renal failure on maintenance hemodialysis. Med Sci Monit 2002;8:CR331–6.
[12] Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol 2001;18:128–47.
[13] Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K. Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord 2006;21:380–4.
[14] Hanly P, Powles P. Hypnotics should never be used in patients with sleep apnea. J Psychosom Res 1993;37(Suppl 1):59–65.
[15] Enomoto M, Eudo T, Suenaga K, Miura N, Nakano Y, Kohtoh S, et al. Newly developed waist actigraphy and its sleep/wake scoring algorithm. Sleep Biol Rhythms 2009;7:17–22.
[16] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–39.
[17] Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. J Psychosom Res 2009;67:109–16.
[18] Ulloa EW, Salup R, Patterson SG, Jacobsen PB. Relationship between hot flashes and distress in men receiving androgen deprivation therapy for prostate cancer. Psychooncology 2009;18:598–605.
[19] Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. Sleep 1994;17:497–501.
[20] Stein MB, Chartier M, Walker JR. Sleep in nondepressed patients with panic disorder: I. Systematic assessment of subjective sleep quality and sleep disturbance. Sleep 1993;16:724–6.
[21] Partinen M. Epidemiology of sleep disorders. In: Kryger M, Roth T, Dement W, editors. Principals and oractice of sleep medicine. 2nd ed. Philadelphia: WB Saunders; 1994. p. 437–52.
[22] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
[23] Kim J, In K, You S, Kang K, Shim J, Lee S, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 2004;170:1108–13.
[24] The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–89.
[25] Enomoto M, Li L, Aritake S, Nagase Y, Kaji T, Tagaya K, et al. Restless legs syndrome and its correlation with other sleep problems in the general population of Japan. Sleep Biol Rhythms 2006;4:153–9.
[26] Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006;35:350–64.
[27] Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res 2004;56: 497–502.
[28] Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, et al. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep 2006;29: 1391–7.
[29] Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. Sleep 2007;30:213–8.
[30] Meissner HH, Riemer A, Santiago SM, Stein M, Goldman MD, Williams AJ. Failure of physician documentation of sleep complaints in hospitalized patients. West J Med 1998;169:146–9.
[31] Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. Sleep 1999;22(Suppl 2):S359–65.
[32] Terzano MG, Parrino L, Cirignotta F, Ferini-Strambi L, Gigli G, Rudelli G, et al. Studio Morfeo: insomnia in primary care, a survey conducted on the Italian population. Sleep Med 2004;5: 67–75.
[33] Aikens JE, Rouse ME. Help-seeking for insomnia among adult patients in primary care. J Am Board Fam Pract 2005;18:257–61.
[34] Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. Pharmacoepidemiol Drug Saf 2002;11:97–104.
[35] Mahoney JE, Webb MJ, Gray SL. Zolpidem prescribing and adverse drug reactions in hospitalized general medicine patients at a Veterans Affairs hospital. Am J Geriatr Pharmacother 2004;2:66–74.
[36] Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005;331:1169.
[37] Chang CM, Wu EC, Chang S, Lin KM. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. Am J Geriatr Psychiatry 2008;16:686–92.

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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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automatic saccades is impaired in schizophrenic patients.[4] One task used to investigate saccade inhibition is the antisaccade task, which requires subjects to inhibit a saccade toward a briefly appearing peripheral target, and to instead immediately generate a saccade to a point in the opposite direction.[5] Antisaccade deficits have high sensitivity and high specificity for the diagnosis of schizophrenia and are thought to be a genetic marker for the illness. Reported rates of antisaccade deficits range from 24% to 71% in patients with schizophrenia and from 2% to 27% in normal controls.[6–9]

Several comparison studies to date have examined the brain regions associated with antisaccade tasks in schizophrenic patients and normal control subjects.[10–12] Most of these have reported reduced activity in the basal ganglia and the cortex, including the prefrontal area, in the schizophrenic group. As we will discuss further below, we question whether the activities of these brain regions were in fact reduced or not. Functional magnetic resonance imaging (fMRI) is a specialized MRI scan that measures hemodynamic responses related to neural activity in the brain. When two actions that generate neural activity are compared in fMRI, an analysis is based on the difference between a baseline signal and a signal measured at the time of task execution. Therefore, when comparing two groups, it is important to be able to assume that the baseline levels in the two groups are equivalent. Most previous fMRI research on antisaccade and saccade tasks used a target that required subjects to focus on a central fixation point during baseline imaging. One possibility is that patients with schizophrenia may exhibit greater cerebral activities during the fixation condition than healthy subjects. In order to examine this baseline effect, here we compared schizophrenic patients and normal subjects using a blank screen on which subjects were not required to focus at baseline.

MATERIALS AND METHODS

Subjects

Eighteen patients with schizophrenia (11 men and 7 women; mean age 34.8 ± 7.9) and 18 healthy subjects (9 men and 9 women; mean age 37.6 ± 4.8) participated in this study. All patients met the criteria for schizophrenia according to the DSM-IV. The mean duration of education was significantly longer ($P < 0.05$) in the healthy subject group than in the schizophrenia group. In the latter group, the mean age at onset of psychosis was 25.8 years old, the mean Brief Psychiatric Rating Scale total score was 41.9, and the mean total dose of antipsychotic medication per patients converted to haloperidol equivalency was 16.0 mg. All healthy subjects were free from neurological or psychiatric illness, and no abnormalities were observed on brain structural MRI. Written informed consent was obtained from all participants. All participants were right-handed according to the Edinburgh Handedness Inventory.[13] This project was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Nihon University School of Medicine.

MRI acquisition

MRI data were acquired using a 1.5T Siemens Symphony system (Siemens, Erlangen, Germany). Gradient-recalled echo planar imaging (EPI) was used for the fMRI sequence to obtain blood oxygen level-dependent contrast. Interleaved multi-slice gradient EPI was used to produce 40 continuous, 3-mm thick axial slices encompassing the entire brain (echo time = 62 ms, repetition time = 4000 ms, flip angle = 90 degrees, field of view = 192 mm, 64*64 matrix). Each series comprised 104 scans with a complete duration of 416 s. The run began with four dummy volumes to allow for T1 equilibration effects. The head of the subject was fixed using cushions to minimize motion artifacts.

Behavioral methods

Saccade and antisaccade performance was recorded outside of the magnet. Horizontal and vertical eye movements and target position were measured using electro-oculography (EOG) (NEC) and a goggles-type display (SONY).

Stimulus projection

The stimulus was generated using a personal computer (OS: Windows 98) and made to order software. The stimulus was projected on a small screen attached to a head coil, using a liquid crystal display projector system customized to our MRI machine (Kiyohara Optics, Tokyo).

Prosaccade task

Each trial began with the target in central fixation (0 degrees) for a random duration of 500–1500 ms.

The target then shifted randomly to left or right horizontal peripheral locations (10 degrees from the center position), where it remained for 1000 ms. The target size was 1 degree of the visual angle. The number of left and right saccadic eye movements was the same. Participants were instructed to follow the target as quickly and accurately as possible, alternating between 40 s of control condition task and 40 s of prosaccade condition, completing 10 sets of trials in all. During the baseline condition, subjects were in total darkness and were asked to maintain fixation and not blink.

Antisaccade task

The parameters for the antisaccade task were identical to those for the prosaccade task. The antisaccade task required participants to fixate the target in the central position and to redirect their gaze in the opposite direction of the target as soon as it shifted to the periphery. Participants performed 10 sets of trials in total, alternating antisaccade and control conditions.

fMRI data analysis

Image analysis was performed using an Ultra5 workstation (Sun Microsystems, Palo Alto, CA, USA) using MATLAB (Mathworks Inc., Natick, MA, USA) and statistical mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Before statistical parametric maps were calculated, EPI images for each time series were realigned to the first functional image to remove residual head movement. Images were then coregistered and normalized to the Montreal National Institute template. Confounding effects of global volume activity and magnetic noise were removed using linear regression and cosine functions (up to a maximum of 1 cycle per 40 scans). Removing the latter confounds corresponds to high-pass filtering of the time series to remove low-frequency artifacts that can arise due to aliased cardiac and other cyclical components. After normalization, three-dimensional spatial smoothing was applied to each volume using a Gaussian kernel of $8 \times 8 \times 8$ mm. Alternating periods of baseline and activation were modeled using a simple delayed box-car reference vector to account for delayed cerebral blood flow after stimulus presentation. Significantly activated pixels were searched for using the General Linear Model approach for time-series data.

To create the subtraction activation image between saccade and antisaccade, data was analyzed using random-effect analysis. Statistical significance was set at the level of $P < 0.001$, uncorrected for multiple comparisons.

Intra-individual comparisons between saccade and antisaccade were analyzed using paired *t*-tests, and statistical significance was set at the level of $P < 0.005$, uncorrected for multiple comparisons.

RESULTS

Behavioral data

Demographic and performance data are summarized in Table 1. The analysis of EOG revealed no differences in prosaccades between the patients and normal controls. In contrast, error rates in antisaccades were higher and latencies of prosaccades and antisaccades were longer in the patient group than in the control group.

fMRI data

Activated areas in the normal control group are shown in Fig. 1a for the saccade tasks and in Fig. 1b for the antisaccade tasks ($P < 0.001$, uncorrected for multiple comparisons). During the saccade tasks, regional activations were observed bilaterally in the frontal eye fields (FEF), supplementary eye fields (SEF), and parietal eye fields (PEF), left lenticular

Table 1. Subjects and eye movement performance

	Patients with Schizophrenia	Control
Number of cases (male/female)	18 (12/6)	18 (9/9)
Age (year)	34.8 ± 7.9	37.6 ± 4.8
Education (year)*	11.2 ± 2.9	15.3 ± 2.2
Age at the onset (year)	25.8 ± 6.4	–
HPD equivalence (mg)	16.0 ± 16.1	–
BPRS total score	41.9 ± 7.9	–
Saccade error (%)*	0.5 ± 0.67	0.00 ± 0.00
Saccade latency (ms)*	212.2 ± 30.1	174.2 ± 11.8
Anti-saccade error (%)*	1.1 ± 1.6	0.14 ± 0.35
Anti-saccade latency (ms)*	244.9 ± 48.4	205.6 ± 18.5

Statistical analysis (T-test) *$P < 0.05$.
BPRS, Brief Psychiatric Rating Scale; HPD, haloperidol.

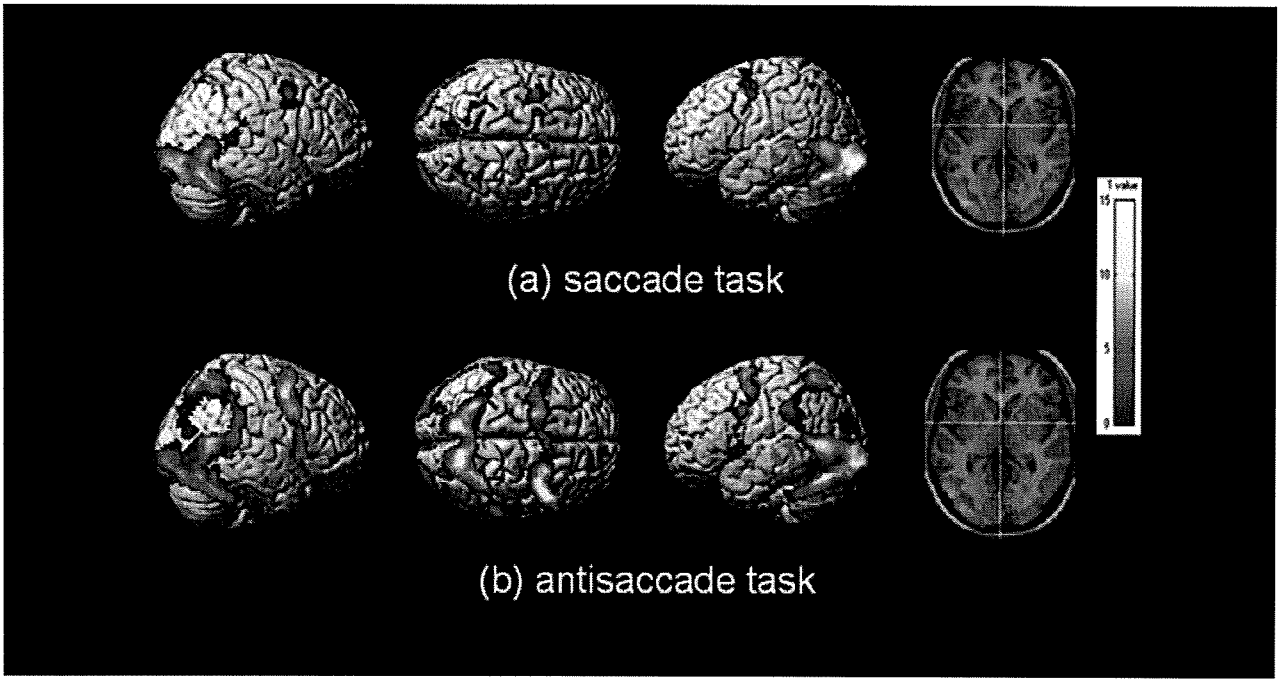

Figure 1. Brain regions displaying greater activities during (a) saccade and (b) antisaccade conditions than during control condition in healthy subjects. In the rightmost image, the activation map is overlaid onto a T1 SPM normalized brain image. The height threshold is set at $P < 0.001$, uncorrected.

nucleus, and bilateral occipital cortices (V1). During the antisaccade tasks, activations were observed in the same regions as during saccade tasks, as well as bilaterally in the inferior parietal lobules (IPL), thalami, right lenticular nucleus, inferior frontal gyrus (IFG), and left dorsolateral prefrontal cortex (DLPFC) (Table 2).

Activation areas in the patient group are shown in Fig. 2a for the saccade tasks and in Fig. 2b for the antisaccade tasks ($P < 0.001$, uncorrected for multiple comparisons). During the saccade task, regional activation was observed bilaterally in the FEF, SEF, and PEF, left lenticular nucleus, and V1. These regions are the same as those seen in the normal subject group. However, the patient group also showed activations in the IFG, DLPFC, IPL, lenticular nucleus and thalamus during saccade tasks. During the antisaccade tasks, activation was observed in the same regions as in the saccade tasks (Table 3).

Furthermore, in the normal control group, comparing brain activity during the antisaccade task with that during the saccade task revealed that antisaccade eye movements induced elevated activities in the bilateral FEF, PEF, IPL, ACC, IFG, and DLPFC ($P < 0.005$, uncorrected for multiple comparisons). In the patient group, however, only bilateral activation in the PEF was observed.

Correlation between fMRI activation and eye movement performance

In order to assess the effect of performance on brain activity, we analyzed the correlation between error rate and brain activity. Figure 3 shows the correlation between fMRI activation and eye movement performance in patients with schizophrenia. fMRI activation is calculated from each peak voxel. No significant correlation was observed between two parameters.

DISCUSSION

Our understanding of human cortical control of saccades is derived from observations of cerebral lesions[14–16] and from transcranial magnetic stimulation,[17,18] positron emission tomography,[19,20] and fMRI.[21–24] Previous studies in these areas have indicated that saccadic eye movements are controlled by

Table 2. Brain regions more active during visually guided saccades and antisaccades than during control tasks in healthy subject

Brain region		Saccade vs rest Coordinate			*t*-value	Antisaccade vs rest Coordinate			*t*-value
		X	*Y*	*Z*		*X*	*Y*	*Z*	
DLPFC	R	–	–	–	NS	*50*	*40*	*–8*	4.01
	L	–	–	–	NS	*–44*	*50*	*4*	4.24
FEF	R	*46*	*6*	*50*	5.34	*40*	*–2*	*50*	5.87
	L	*–40*	*–6*	*50*	6.08	*–38*	*–4*	*52*	6.52
SEF	R	*6*	*6*	*62*	4.20	*8*	*8*	*52*	4.20
	L	*–4*	*4*	*60*	5.87	*–2*	*10*	*46*	5.56
PEF	R	*32*	*–54*	*48*	3.80	*26*	*–58*	*54*	6.70
	L	*–30*	*–56*	*56*	4.28	*–26*	*–60*	*52*	7.91
IPL	R	–	–	–	NS	*64*	*–36*	*28*	6.14
	L	–	–	–	NS	*–64*	*–40*	*34*	5.75
Thalamus	R	–12	–18	10	3.96	*10*	*–14*	*8*	8.30
	L	–10	–18	–2	6.53	*–10*	*–16*	*8*	6.29

DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IPL, inferior parietal lobule; L, left; NS, not significant; PEF, parietal eye fields; R, right; SEF, supplementary eye fields.

a cortical network that includes the PEF, located in the intraparietal sulcus and superior parietal lobule, the FEF, located in the precentral gyrus, and the SEF, located in the upper medial wall of the frontal lobe. Activation has also been observed in the bilateral dorsolateral prefrontal cortices, supramarginal gyri, anterior cingulate cortices, and thalami during antisaccade tasks.[25] In short, in normal subjects no

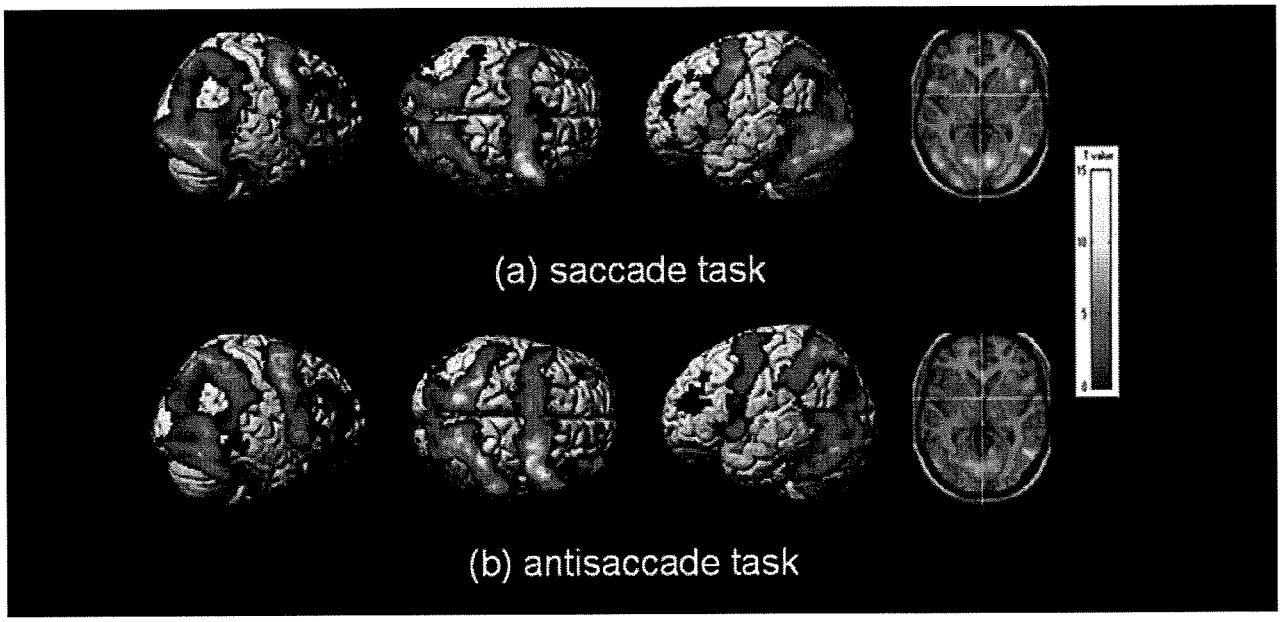

Figure 2. Brain regions displaying greater activities during (a) saccade and (b) antisaccade conditions than during control conditions in patients with schizophrenia. In the rightmost image, the activation map is overlaid onto a T1 SPM normalized brain image. The height threshold is set at $P < 0.001$, uncorrected.

Table 3. Brain regions more active during visually guided saccades and antisaccades than during control tasks in patients with schizophrenia

		Saccade vs rest Coordinate				Antisaccade vs rest Coordinate			
Brain region		*X*	*Y*	*Z*	*t*-value	*X*	*Y*	*Z*	*t*-value
DLPFC	R	*36*	*56*	*26*	8.80	*42*	*56*	*8*	6.05
	L	−38	54	14	4.26	*−36*	*44*	*12*	5.00
FEF	R	*34*	*2*	*64*	8.52	*26*	*0*	*48*	12.06
	L	*−44*	*−4*	*58*	9.91	*−36*	*−6*	*46*	8.99
SEF	R	*12*	*16*	*38*	5.38	*10*	*4*	*48*	5.30
	L	*−8*	*22*	*38*	5.23	*−12*	*0*	*46*	5.53
PEF	R	*30*	*−54*	*48*	7.25	*22*	*−60*	*54*	12.32
	L	*−28*	*−52*	*50*	10.71	*−28*	*−52*	*56*	12.89
IPL	R	56	−32	22	8.63	*62*	*−38*	*18*	5.09
	L	−58	−40	22	3.77	*−62*	*−38*	*18*	4.27
Thalamus	R	12	−14	2	6.70	*10*	*−18*	*−4*	7.09
	L	−12	−14	−2	6.92	*−12*	*−16*	*2*	6.23

DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IPL, inferior parietal lobule; L, left; PEF, parietal eye fields; R, right; SEF, supplementary eye fields.

activation of DLPFC, IFG, striatum, and thalamus were observed during the saccade tasks.

Contrary to previous reports, the present study showed the activations in the DLPFC, IFG, striatum, and thalamus during both the saccade and antisaccade tasks in patients with schizophrenia. In addition, differential activation maps between the antissacade and saccade tasks exhibited the bilateral activation of the FEF, PEF, IPL, ACC, IFG, and DLPFC in normal subjects, whereas only the PEF were activated bilaterally in the patient group. These results show that normal subjects process the saccade and antisaccade tasks in different brain regions, whereas patients with schizophrenia likely use virtually the same regions when processing both tasks. In the patient group, therefore, when brain activations during eye movement tasks were compared directly, the elevated activations of the DLPFC and thalamus normally seen in antisaccade tasks relative to saccade tasks were no longer observed. In comparing the patients to the normal controls, the present study demonstrated higher activity of the thalamus and broad cortical regions (including the prefrontal area), especially during saccade tasks. This suggests hyperactivation, not reduced activation, in the prefrontal cortex and thalamus in patients with schizophrenia. Taken together, though the antisaccade task is cognitively more demanding than the saccade task, these regions in the patients with schizophrenia did not seem to be activated at a level that corresponded to the degree of difficulty of the tasks presented.

The tasks used in most of the previous studies required subjects to focus on a gazing point, and the reduced activities of the DLPFC and thalamus were observed during the antisaccade tasks in patients with schizophrenia. Three recent studies using fMRI revealed reduced activation in the right DLPFC and reduced activation in the striatum in schizophrenia.[10–12]

In contrast, our results showed higher activities in broad cortical and subcortical regions during the saccade and antisaccade tasks in the patient group as compared with the normal control group. This suggests that these regions could already be activated by the time the schizophrenic patient focuses on the gazing point; therefore, the difference in activation levels between baseline and eye movements becomes smaller in the patient group.

In the present study, we demonstrated the activations in the DLPFC and thalamus during the saccade task in the patient group. The fronto-striato-thalamocortical network,[26–28] including the prefrontal cortex and thalamus, is important for control of antisaccades. Schizophrenia presents with dysfunction in dopaminergic neural networks[29] and the fronto-striato-thalamic circuit.[30,31] Dysfunction in the

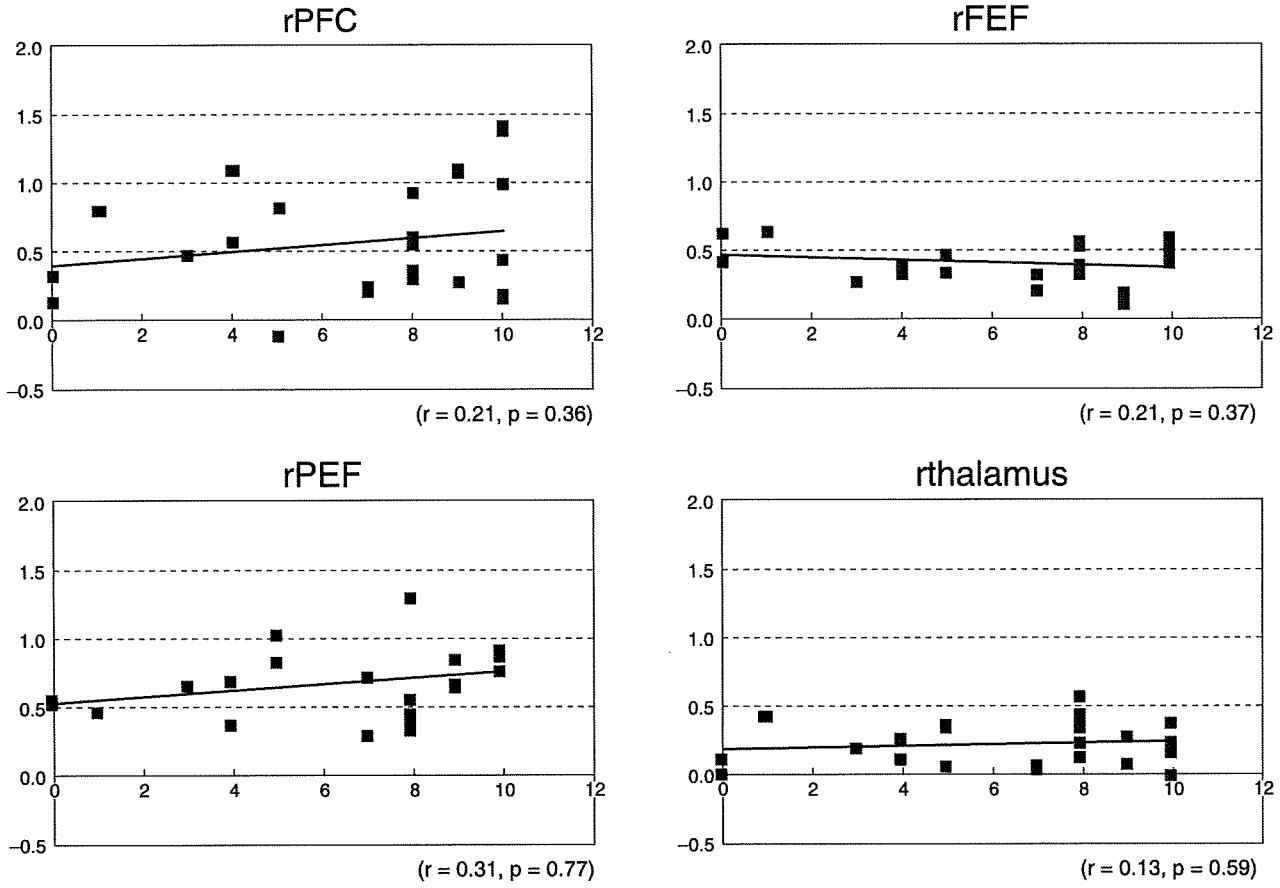

Figure 3. The correlation between brain activation and the number of antisaccade errors. The horizontal axis represents the number of antisaccade errors, and the vertical axis represents the estimated magnetic resonance imaging signal. rFEF, right frontal eye fields; rPEF, right parietal eye fields; rPFC, right prefrontal cortex; rthalamus, right thalamus.

striato-thalamo-cortical dopaminergic circuitry may reduce inhibition of reflexive saccade and thus facilitate saccades for the target direction during the antisaccade task in schizophrenics. Our results indicate that this dysfunction has an important influence on subtle motor control and therefore affects antisaccade generation through both the direct and indirect basal ganglia pathways. These findings suggest that patients with schizophrenia who display antisaccade inhibition errors may present with dysfunction in the fronto-striato-thalamo-cortical network.

Given that previous studies have targeted patients with schizophrenia with poor performance in cognitive tasks, a bias toward reduced brain activations may have been present.[32–36] In order to assess the effect of performance on brain activity, we analyzed the correlation between error rate and brain activity. No significant correlation was observed between the two variables. Therefore, we conclude that the performance did not directly affect the results.

CONCLUSION

In order to examine baseline effect, we employed an eye movement task that did not require subjects to focus on a fixation point during the baseline condition, and compared brain activity between patients with schizophrenia and normal control subjects. In normal subjects, activities in the DLPFC and thalamus were greater during antisaccade tasks than during saccade tasks, whereas no significant difference was observed in patients with schizophrenia. These results suggest that the brains of patients with schizophrenia did not seem to be activated at a level that corresponded to the degree of difficulty of the tasks presented. Previous studies that used target fixa-

tion at baseline assessment showed reduced activities of the DLPFC and thalamus in patients. In contrast, our study demonstrated hyperactivation of the DLPFC and thalamus in patients, suggesting that in patients with schizophrenia these brain regions were already activated by the time patients viewed a fixed target at baseline. We think that these results reflect the symptom that patients of schizophrenia can not adapt to the environment. Finally, we suspect that patients with schizophrenia may be affected by a defect in the fronto-striato-thalamo-cortical network associated with motor function control.

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REFERENCES

[1] Iacono WG, Tuason VB, Johnson RA. Dissociation of smooth-pursuit and saccadic eye tracking in remitted schizophrenics. An ocular reaction time task that schizophrenic perform well. *Arch. Gen. Psychiatry* 1981; 38: 991–996.

[2] Levin S, Holzman PS, Rothenberg SJ, Lipton RB. Saccadic eye movements in psychotic patients. *Psychiatry Res.* 1981; 5: 47–58.

[3] Levin S, Jones A, Stark L, Merrin EL, Holzman PS. Identification of abnormal patterns in eye movements of schizophrenic patients. *Arch. Gen. Psychiatry* 1982; 39: 1125–1130.

[4] Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biol. Psychiatry* 1988; 23: 670–677.

[5] Everling S, Fischer B. The antisaccade: A review of basic research and clinical studies. *Neuropsychologia* 1998; 36: 885–899.

[6] Sereno AB, Holzman PS. Antisaccades and smooth pursuit eye movements in schizophrenia. *Biol. Psychiatry* 1995; 37: 394–401.

[7] McDowell JE, Clementz BA. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: Studies of diagnostic specificity. *Exp. Brain. Res.* 1997; 115: 333–344.

[8] Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I. Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. *J. Psychiatr. Res.* 1990; 24: 9–24.

[9] Crawford TJ, Sharma T, Puri BK, Murray RM, Berridge DM, Lewis SW. Saccadic eye movements in families multiply affected with schizophrenia: The Maudsley Family Study. *Am. J. Psychiatry* 1998; 155: 1703–1710.

[10] Raemaekers M, Jansma JM, Cahn W *et al.* Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Arch. Gen. Psychiatry* 2002; 59: 313–320.

[11] McDowell JE, Brown GG, Paulus M *et al.* Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol. Psychiatry* 2002; 51: 216–223.

[12] Tu PC, Yang TH, Kuo WJ, Hsieh JC, Su TP. Neural correlates of antisaccade deficits in schizophrenia, an fMRI study. *J. Psychiatry Res.* 2006; 40: 606–612.

[13] Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 1971; 9: 97–113.

[14] Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp. Brain Res.* 1985; 58: 455–472.

[15] Evdokimidis I, Liakopoulos D, Constantinidis TS, Papageorgiou C. Cortical potentials with antisaccades. *Electroencephalogr. Clin. Neurophysiol.* 1996; 98: 377–384.

[16] Crevits L, Hanse MC, Tummers P, Van Maele G. Antisaccades and remembered saccades in mild traumatic brain injury. *J. Neurol.* 2000; 247: 179–182.

[17] Kapoula Z, Isotalo E, Müri RM, Bucci MP, Rivaud-Péchoux S. Effects of transcranial magnetic stimulation of the posterior parietal cortex on saccades and vergence. *Neuroreport* 2001; 12: 4041–4046.

[18] Leff AP, Scott SK, Rothwell JC, Wise RJ. The planning and guiding of reading saccades: A repetitive transcranial magnetic stimulation study. *Cereb. Cortex.* 2001; 11: 918–923.

[19] Anderson TJ, Jenkins IH, Brooks DJ, Hawken MB, Frackowiak RS, Kennard C. Cortical control of saccades and fixation in man. A PET study. *Brain* 1994; 117: 1073–1084.

[20] O'Driscoll GA, Wolff AL, Benkelfat C, Florencio PS, Lal S, Evans AC. Functional neuroanatomy of smooth pursuit and predictive saccades. *Neuroreport* 2000; 11: 1335–1340.

[21] Gaymard B, Ploner CJ, Rivaud-Péchoux S, Pierrot-Deseilligny C. The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Exp. Brain Res.* 1999; 129: 288–301.

[22] Connolly JD, Goodale MA, Desouza JF, Menon RS, Vilis T. A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *J. Neurophysiol.* 2000; 84: 1645–1655.

[23] Nobre AC, Gitelman DR, Dias EC, Mesulam MM. Covert visual spatial orienting and saccades: Overlapping neural systems. *Neuroimage* 2000; 11: 210–216.

[24] Matsuo K, Kato C, Sumiyoshi C *et al.* Discrimination of Exner's area and the frontal eye field in humans: Functional magnetic resonance imaging during language and saccade tasks. *Neurosci. Lett.* 2003; 340: 13–16.
[25] Matsuda T, Matsuura M, Ohkubo T *et al.* Functional MRI mapping of brain activation during visually guided saccades and antisaccades: Cortical and subcortical networks. *Psychiatry Res. Neuroimaging.* 2004; 131: 147–155.
[26] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 1986; 9: 357–381.
[27] Petit L, Orssaud C, Tzourio N, Salamon G, Mazoyer B, Berthoz A. PET study of voluntary saccadic eye movements in humans: Basal ganglia-thalamocortical system and cingulate cortex involvement. *J. Neurophysiol.* 1993; 69: 1009–1017.
[28] McFarland NR, Haber SN. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J. Neurosci.* 2002; 22: 8117–8132.
[29] Gerfen CR, Engber TM, Mahan LC *et al.* D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 1990; 250: 1429–1432.
[30] Buchsbaum MS, Haier RJ, Potkin SG *et al.* Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. *Arch. Gen. Psychiatry* 1992; 49: 935–942.
[31] Camchong J, Dyckman KA, Chapman CE, Yanasak NE, McDowell JE. Basal ganglia-thalamocortical circuitry disruptions in schizophrenia during delayed response tasks. *Biol. Psychiatry* 2006; 60: 235–241.
[32] Frith CD, Friston KJ, Herold S *et al.* Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br. J. Psychiatry* 1995; 167: 343–349.
[33] Price CJ, Friston KJ. Scanning patients with tasks they can perform. *Hum. Brain Mapp.* 1999; 8: 102–108.
[34] Bullmore E, Brammer M, Williams SC *et al.* Functional MR imaging of confounded hypofrontality. *Hum. Brain Mapp.* 1999; 8: 86–91.
[35] Callicott JH, Bertolino A, Mattay VS *et al.* Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb. Cortex.* 2000; 10: 1078–1092.
[36] Jansma JM, Ramsey NF, Coppola R, Kahn RS. Specific versus nonspecific brain activity in a parametric N-back task. *Neuroimage* 2000; 12: 688–697.

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Epileptic, organic and genetic vulnerabilities for timing of the development of interictal psychosis

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Background
Age at the first psychotic episode and an interval between the onset of epilepsy and that of psychosis reflect developmental processes of interictal psychosis. However, factors relating to these indices remain unknown.

Aims
To identify clinical variables that are associated with the timing of the development of interictal psychosis.

Method
In 285 adults with epilepsy with interictal psychosis, effects of epileptic (epilepsy type), organic (intellectual functioning) and genetic (family history of psychosis) variables on timing of the development of psychosis were examined.

Results
The mean interval between the onset of epilepsy and that of psychosis was 14.4 years. Some psychosis occurred within a few years of the first seizure. Generalised epilepsy, normal intellectual function and a positive family history of psychosis were associated with early onset of psychosis.

Conclusions
Early development of interictal psychosis in people with epilepsy may reflect other individual vulnerabilities to psychosis rather than epilepsy-related damage.

Declaration of interest
None.

Interictal psychosis in epilepsy was first studied systematically by Slater and his colleagues.[1] They reported three main pieces of evidence to delineate interictal psychosis (called schizophrenia-like psychosis in the paper) as a distinct entity from schizophrenia: psychopathological characteristics, psychosis occurring after the development of epilepsy and no genetic loading for schizophrenia. Subsequent studies have formed a general consensus that interictal psychosis is mainly related to various epilepsy-related factors such as type of epilepsy, seizure types and laterality and locality of electroencephalogram (EEG) abnormalities, rather than non-specific demographic factors.[2] However, studies on interictal psychosis have shown contradictive findings that some of the demographic characteristics such as intellectual function[3,4] and family history of psychosis[5] were associated with occurrence of interictal psychosis. This is similar to the positive associations between these demographic factors and a high risk of functional psychoses such as schizophrenia. Using a comprehensive, multicentre database of patients suffering from epilepsy with and without psychosis, our group has found that interictal psychosis occurred more frequently in individuals with certain risk factors, including partial epilepsies, complex partial seizures, generalised tonic–clonic seizures, earlier onset of epilepsy and borderline intellectual function.[6] Most of these risk factors were also common in different types of epilepsy psychoses (e.g. interictal, postictal and bimodal psychoses),[7] but some factors historically known as risk factors for interictal psychosis were not extracted with multivariate analyses because they overlapped or interacted with others.[6–8]

Age at the time of the first psychotic episode and the time interval between the onset of epilepsy and that of psychosis are key elements of studies in interictal psychosis, as these age-related variables likely reflect neurodevelopmental and/or neurodegenerative processes in the brain.[9] Indeed, Slater *et al*[1] showed that patients with interictal psychosis tend to suffer their first seizure in early adolescence, with psychosis developing in their late twenties or thirties (approximately 15 years after the onset of epilepsy). They interpret the long interval, during which epilepsy and its consequences could cause further damage to the brain, as a preparatory period for generation of psychosis. Whereas many studies have reported similar age-related variables,[2] some have suggested the interval is an artefact as a result of the wide range of distribution of time intervals and to the tendency of a shorter interval in individuals with late-onset epilepsy.[10,11] In our previous study,[12] age at onset of psychosis in a subgroup of patients with chronic interictal psychosis was comparable with that in those with schizophrenia, whereas the age at onset was more advanced in the whole group of patients with interictal psychosis (both episodic and chronic). We also showed no difference between various types of partial epilepsies in age at onset of psychosis and in time intervals.[8] However, few studies have examined the contributions of the other clinical factors to age-related variables; thus, it remains unknown whether particular clinical factors are related to the timing of development of interictal psychosis. In the current study, we investigated the timing of development of interictal psychosis in association with epilepsy-related and demographic characteristics in a large cohort of patients with interictal psychosis.

Method

Definition of interictal psychosis

In our study, psychosis was defined as the presence of hallucinations, delusions or a limited number of severe abnormalities of behaviour in accordance with the ICD–10.[13] The operational criteria for interictal psychosis were as follows: the psychosis developed after the onset of epilepsy;[1,14,15] the psychotic episodes occurred with no distinct antecedent seizures when the patient was seizure-free or between habitual seizures;[6,7] psychotic episodes lasted 24 h or more in a state of full consciousness. Interictal

psychosis included chronic schizophrenia-like psychosis (at least one episode lasting 1 month or more) and brief (acute, episodic) interictal psychosis (all episodes resolved within 1 month).[1,16–18] Postictal psychosis, which occurred within 7 days after a decisive seizure or cluster of seizures,[7,17,19] and ictal psychotic phenomenon[17] were excluded.

Participants

All participants met the criteria for epilepsy as set forth in the 1989 International Classification of Epilepsies and Epileptic Syndromes.[20] The participants all attended one of five institutions with adult epilepsy clinics: National Centre Hospital for Mental, Nervous, and Muscular Disorders; Nihon University Hospital; Tokyo Medical University Hospital; Tokyo Medical and Dental University Hospital; or Komagino Hospital. The five epilepsy clinics cover the greater Tokyo area of a population of approximately 35 million as the main neuropsychiatric institutions for adults with epilepsy. In addition, the National Centre Hospital is the only institution in the country that has a neuropsychiatric in-patient unit dedicated to patients with epilepsy, accepting tertiary referrals from outside the catchment area. Since August 1996, these epilepsy clinics have maintained a collaborative database designed specifically for epilepsy psychosis.[6–8,12] Our previous studies[6–8,12] were based on the database with patients who had been registered until the end of 1996. The current study was conducted with a data-set entered until December 2000, with a total of 313 patients with epilepsy and interictal psychotic episodes being identified. To focus on interictal psychosis, 19 patients with bimodal psychosis, who exhibited both interictal and postictal psychoses in distinct periods,[7] were excluded from the study. Five patients with epilepsy resulting from a neurodegenerative disorder and four without sufficient clinical information regarding the epilepsy were also excluded. Consequently, 285 patients with interictal psychosis were enrolled in the study. No participants showed evidence of substance misuse, dementing process or a recent progressive space-occupying lesion.

Variables studied

We investigated the following variables:

(a) age at the time of investigation;

(b) gender;

(c) family history of psychosis, i.e. any psychotic disorder (schizophrenia, other paranoid disorder, acute transient psychosis, etc.) in a first-degree relative, according to the Japanese version of the Family History Research Diagnostic Criteria;[21]

(d) age at the onset of epilepsy, i.e. age at the time of the first afebrile seizure;

(e) type of epilepsy based on ictal symptoms, EEG findings and neuroimaging in accordance with the International Classification of Epilepsies and Epileptic Syndromes[20] (i.e. localisation-related epilepsies and generalised epilepsies, including idiopathic and symptomatic);

(f) intellectual functioning: impaired (full-scale IQ on the Wechsler Adult Intelligence Scale–Revised[22] of 70 or below), borderline (of 71–84), or normal (of 85 or above) in accordance with the DSM–IV;[23]

(g) age at onset of psychosis (i.e. age at the time of the first psychotic episode);

(h) time interval between the onset of epilepsy and that of psychosis, calculated as age at onset of psychosis minus age at onset of epilepsy.

As different neuroimaging techniques were used during different time periods and by each institution, neuroimages were used only for diagnostic information. Diagnoses and evaluations were made by consultant neuropsychiatrists qualified in both psychiatry and epileptology. The study was approved by the ethics committees of the institutions.

Data analysis

Differences in linear variables (ages) for the categorical variables (gender, epilepsy type and family history) were subjected to analysis of variance (ANOVA). Correlation between categorical variables was examined by means of the chi-squared test or Fisher's exact test. Correlations between linear or rank-order variables (intellectual functioning) were examined by means of simple regression analysis or Spearman's rank-order correlation coefficient. Because age at the time of examination was correlated significantly with the other age-related variables (age at the onset of epilepsy ($r=0.39$, $P<0.0005$), time interval ($r=0.31$, $P<0.0005$), and age at the onset of psychosis ($r=0.62$, $P<0.0005$)), the weighted least squares procedure (weighted by age at the time of examination) was applied.[12] A P-value of <0.05 was considered significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 14.0 for Windows.

Results

Clinical characteristics of the 285 patients with interictal psychosis were as follows: mean age at the time of examination was 40.7 years (s.d. = 12.8, range 19–76, median 39). There were 146 men and 139 women. A total of 236 patients had localisation-related epilepsies and 49 generalised epilepsies (34 with idiopathic and 15 with symptomatic generalised epilepsies). With respect to estimated aetiologies of epilepsy, there were 22 patients with central nervous system infections, 26 with birth complications (including cerebral palsy), 15 with head trauma, 7 with brain tumours, 16 with migration disorders or other malformation, 5 with vascular disorders, and pathogenesis was unknown for the remaining 194 patients. Intellectual function was normal in 140 patients, borderline in 55, and impaired in 90. There were 244 patients with chronic schizophrenia-like psychosis, 27 with brief interictal psychosis and 14 with interictal psychosis of unknown duration. Twenty-one patients had a family history of psychosis.

Distributional relations between the patients' characteristics studied were as follows: gender and intellectual functioning ($\chi^2=2.6$, $P=0.280$), gender and epilepsy type (129 men and 107 women with localisation-related epilepsies, 17 men and 32 women with generalised epilepsies; $\chi^2=5.7$, $P=0.017$), gender and family history of psychosis ($\chi^2=0.11$, $P=0.736$), intellectual functioning and epilepsy type ($\chi^2=4.1$, $P=0.126$), intellectual functioning and family history of psychosis ($\chi^2=0.44$, $P=0.802$), and epilepsy type and family history of psychosis ($\chi^2=0.06$, $P=0.767$).

Age-related factors observed were as follows: mean age at onset of epilepsy was 11.7 years (s.d = 8.0, range 0–51, median 11), mean age at onset of psychosis was 26.1 years (s.d. = 9.6, range 12–65, median 24) and the mean time interval between the onset of epilepsy and that of psychosis was 14.4 years (s.d. = 9.3, range 0–51, median 13). Distribution of the time intervals for the entire patient group are shown in Fig. 1. Age at onset of psychosis correlated significantly with that of epilepsy ($r=0.47$, $P<0.0005$) and with the time interval ($r=0.64$, $P<0.0005$).