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IV. 研究成果の刊行物・別刷

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

Naoto Adachi, Nozomi Akanuma, Masumi Ito, Masaaki Kato, Tsunekatsu Hara, Yasunori Oana, Masato Matsuura, Yoshiro Okubo and Teiichi Onuma

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 ($r = 0.39$, P5 0.0005), time interval ($r = 0.31$, P5 0.0005), and age at the onset of psychosis ($r = 0.62$, P5 0.0005)), the weighted least squares procedure (weighted by age at the time of examination) was applied.[12] A P-value of 5 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 ($w^2 = 2.6$, $P = 0.280$), gender and epilepsy type (129 men and 107 women with localisation-related epilepsies, 17 men and 32 women with generalised epilepsies; $w^2 = 5.7$, $P = 0.017$), gender and family history of psychosis ($w^2 = 0.11$, $P = 0.736$), intellectual functioning and epilepsy type ($w^2 = 4.1$, $P = 0.126$), intellectual functioning and family history of psychosis ($w^2 = 0.44$, $P = 0.802$), and epilepsy type and family history of psychosis ($w^2 = 0.06$, $P = 0.767$).

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 ($r = 0.47$, P5 0.0005) and with the time interval ($r = 0.64$, P5 0.0005).

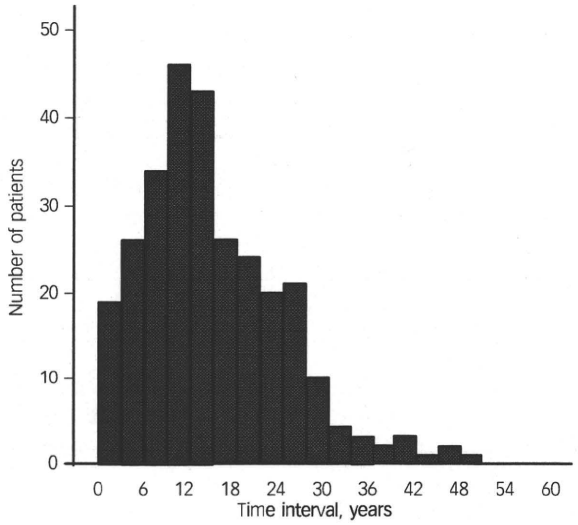

Fig. 1 Distribution of the time intervals (years) between the onset of epilepsy and that of interictal psychosis (mean 14.4 years, s.d. = 9.2, range 0–51, median 13).

The time interval was 3 years or less in 31 patients (10.9%), 5 years or less in 45 (15.8%), 10 years or less in 101 (38.6%).

The time interval also correlated significantly with age at onset of epilepsy (r = 7 0.38, P5 0.0005).

The estimated marginal means of age at onset of epilepsy, age at onset of psychosis and the time interval for each variable are shown in Table 1. The time interval and age at onset of psychosis differed significantly between epilepsy types: interictal psychosis developed at an earlier age and with a shorter interval in patients with generalised epilepsies, in particular with idiopathic generalised epilepsies, than those in patients with localisation-related epilepsies. Intellectual functioning correlated significantly with age at onset of epilepsy and the time interval: the onset of epilepsy was earlier and the interval was longer in those patients with intellectual disturbances than in those without. The onset of psychosis was significantly earlier in patients with a family history of psychosis than in those without.

We carried out further analyses on the participants with localisation-related epilepsies (n = 236) and obtained similar tendencies: intellectual functioning correlated significantly with age at onset of epilepsy (r = 0.293, P5 0.0005; impaired, estimated marginal mean 9.3 (s.e. = 1.1), borderline 11.3 (s.e. = 1.2), normal 15.3 (s.e. = 0.8)), with age at onset of psychosis (r = 0.128, P = 0.049; impaired 26.3 (s.e. = 1.4), borderline 29.8 (s.e. = 1.6), normal 30.0 (s.e. = 1.0)) or with time interval (r = 7 0.157, P = 0.016; impaired 17.0 (s.e. = 1.2), borderline 18.5 (s.e. = 1.4), normal 14.6 (s.e. = 0.9)). Likewise, in the family history of psychosis of the participants with localisation-related epilepsies, the estimated marginal mean age at onset of psychosis also differed significantly (F = 5.45, P = 0.020; positive 22.7 (s.e. = 2.8), negative 29.4 (s.e. = 0.8)). However, there was no significant difference in age at onset of epilepsy (F = 1.33, P = 0.250; positive 10.3 (s.e. = 2.3), negative 13.0 (s.e. = 0.6)) or in time interval (F = 2.33, P = 0.129; positive 12.4 (s.e. = 2.5), negative 16.4 (s.e. = 0.7)).

Discussion

In the current study, age at onset of interictal psychosis and time interval between onset of epilepsy and that of psychosis varied

Table 1 Estimated marginal mean (standard error, 95% CI) years for age-related variables per clinical variables (total *n* = 285)

		Age at onset of epilepsy				Age at onset of psychosis				Time interval			
	n	Mean (s.e.)	95% CI	Test statistic	*P*	Mean (s.e.)	95% CI	Test statistic	*P*	Mean (s.e.)	95% CI	Test statistic	*P*
Gender[a]				*F* = 0.15	0.696			*F* = 0.00	0.984			*F* = 0.09	0.765
Men	146	12.5 (0.7)	11.1–13.9			27.9 (0.9)	26.2–29.7			15.4 (0.8)	13.8–17.1		
Women	139	12.9 (0.7)	11.4–14.3			28.0 (0.9)	26.2–29.8			15.1 (0.8)	13.4–16.7		
Intellectual functioning[b]				r = 0.305	5 0.0005			r = 0.106	0.074			r = 7 0.167	0.005
Impaired	90	9.6 (0.9)	7.8–11.4			25.6 (1.2)	23.3–27.9			16.1 (1.1)	14.0–18.3		
Borderline	55	11.4 (1.1)	9.2–13.6			29.1 (1.4)	26.3–32.0			17.8 (1.3)	15.2–20.4		
Normal	140	15.0 (0.7)	13.6–16.4			28.8 (0.9)	27.1–30.6			13.8 (0.8)	12.2–15.4		
Epilepsy type[a]				*F* = 0.25	0.615			*F* = 13.2	5 0.0005			*F* = 12.0	0.001
Localisation-related epilepsies	236	12.8 (0.6)	11.7–13.9			29.1 (0.7)	27.8–30.5			16.2 (0.6)	15.0–17.5		
Generalised epilepsies	49	12.1 (1.3)	9.5–14.7			22.8 (1.6)	19.6–26.0			10.6 (1.5)	7.7–13.6		
Idiopathic	34	12.7 (1.0)	10.6–14.8			22.5 (1.0)	20.5–24.6			9.8 (1.3)	7.1–12.5		
Symptomatic	15	10.7 (1.5)	7.6–13.8			23.0 (1.5)	20.0–26.0			12.3 (1.9)	8.4–16.2		
Family history of psychosis[a]				*F* = 1.23	0.268			*F* = 5.33	0.022			*F* = 2.28	0.132
Positive	21	10.6 (1.9)	6.8–14.4			22.6 (2.4)	17.9–27.3			12.0 (2.2)	7.6–16.4		
Negative	264	12.8 (0.5)	11.8–13.9			28.4 (0.7)	27.1–29.7			15.5 (0.6)	14.3–16.7		

a. By analysis of variance with weighted least squares procedure (weighted for age at the examination).
b. By Spearman rank-order correlation coefficient.

considerably. Participants with generalised epilepsy, normal intellectual function or a positive family history of psychosis tended to show an early onset of interictal psychosis.

Distribution of the time interval

The mean interval between the onset of epilepsy and that of psychosis was 14.4 years, consistent with previously reported data.[1,2] This interval varied widely among patients, not showing a simple bell-curve distribution. The wide variation may be in part accounted for by the cumulative effects of various epilepsy-related factors on the development of interictal psychosis, i.e. repeated seizures, frequent epileptic discharges in the brain, adverse effects of anti-epileptic drugs and psychosocial stress.[2,18] However, it is important to note that interictal psychosis developed in a considerable number of patients shortly after their first epileptic event (within a few years). Indeed, this fact has been described in previous studies.[1,11] It is not likely that such quick development of interictal psychosis is as a result of the epilepsy-related process alone. There is little evidence that occurrence of interictal psychotic symptoms is precipitated by a higher impact of particular epilepsy processes (e.g. excessive seizures and extensive epileptogenesis),[17] although severe epilepsy can be a risk factor for the development of psychosis. Thus, in addition to the epilepsy-related process, the presence of certain preparatory conditions, such as individual vulnerabilities to psychosis[24] that may be common to organic psychoses or even functional psychoses, may play a role in generating psychotic symptoms in individuals with epilepsy.

Epilepsy type

The interval between onset of epilepsy and that of psychosis was significantly shorter in patients with generalised epilepsies than in those with localisation-related epilepsies, with the onset of epilepsy being comparable among these two groups. Patients with generalised epilepsies, unlike those with localisation-related epilepsies, tend to have fewer epilepsy (organic)-related risk factors for psychosis, i.e. no distinct brain insult, low seizure frequency, simple medications and normal cognitive functioning, which may be associated with a reduced frequency of development of interictal psychosis.[2,6] It is possible that patients with generalised epilepsies in whom interictal psychosis develops might be affected by non-epileptic precipitators of psychosis. This may be similar to the difference between patients with schizophrenia and those with epilepsy; psychosis is observed at a more advanced age in patients with epilepsy than in patients with schizophrenia that does not involve distinct brain damage.[12] Among patients with generalised epilepsies, only those with a strong vulnerability may suffer interictal psychosis at an early age regardless of acquired brain insults because of epilepsy.

Intellectual functioning

Our patients with normal intellectual functioning exhibited interictal psychosis sooner after the onset of epilepsy. This finding was also seen in the subgroup of participants with localisation-related epilepsies only. Impaired intellectual function is often associated with severe epilepsy and brain damage,[25] although it is also observed in people without such conditions.[26] Functional psychosis develops two to three times more frequently in people with impaired intellectual functioning than is reported in the general population.[26,27] Moreover, psychosis develops 1.3–4.7 times more frequently in patients with epilepsy with impaired intellectual functioning than in those without.[7] In contrast, normal intellectual functioning usually suggests having less brain damage and is not related to increased risks for the development of psychosis. Why do patients with a lower risk suffer psychosis earlier than those at a higher risk? Again, psychosis may develop more quickly in patients with normal intellectual functioning who have strong congenital vulnerabilities to psychosis than in those with acquired organic precipitators, i.e. intellectual dysfunction and epilepsy, but without such vulnerabilities.

Family history of psychosis

We have shown that interictal psychosis develops at an earlier age in patients with a family history of psychosis than in those without. A genetic tendency towards psychosis in patients with epilepsy has long been underestimated[2] since Slater's initial study.[1] However, large studies have shown that genetic factors play a significant role in the development of psychosis in patients with epilepsy.[5,6] These findings appear to be similar to those found in functional psychosis (i.e. schizophrenia); people with a positive family history tend to have a higher risk of psychosis and to exhibit their first psychotic symptoms earlier than those without.[28,29] A positive family history of psychosis may be a universal risk factor for developing psychosis, and it appears to reflect, at least in part, a congenital vulnerability to psychosis.[23] Even in patients with epilepsy and a positive family history of psychosis, psychotic symptoms are likely generated sooner regardless of acquired risk factors related to either epilepsy or brain damage.

Study limitations

Some limitations should be considered in relation to the current study. Analysis of age at onset of psychosis in patients with epilepsy is subject to some methodological issues.[10] Because epilepsy psychosis was defined operationally as psychosis developing after the onset of epilepsy in accordance with Slater & Roth's definition,[14] two patient groups were excluded: patients in whom psychosis developed before epilepsy[17] and patients in whom novel psychoses will develop after the time of the investigation or who died before the possible development of psychosis. However, neither group would have been large enough to markedly influence mean age at onset of psychosis or the mean time interval between onsets of the two disorders. Neither of these omissions explains the significant differences in age at onset of psychosis or in the onset interval between patients with particular clinical characteristics. In addition, despite the large cohort of participants with interictal psychosis, the number of patients in whom particular factors were analysed, such as a positive family history of psychosis and generalised epilepsies, was insufficient to produce strong statistical power. Factors that we did not consider may be associated with age-related factors, but would not have affected the result of our study. Although our findings point to the effects of certain vulnerabilities to psychosis (reflected by a positive family history), it is still unclear what these vulnerabilities are. Evidence supporting such vulnerability concepts is scarce, even for patients with functional psychosis.[24]

Results of the current study show some relationship between age at onset of interictal psychosis and several clinical variables that may reflect individual vulnerabilities. These vulnerabilities, in addition to epilepsy-related deficits, can affect the generation of interictal psychosis independently or interactively. Further comprehensive studies to confirm such vulnerabilities are required.

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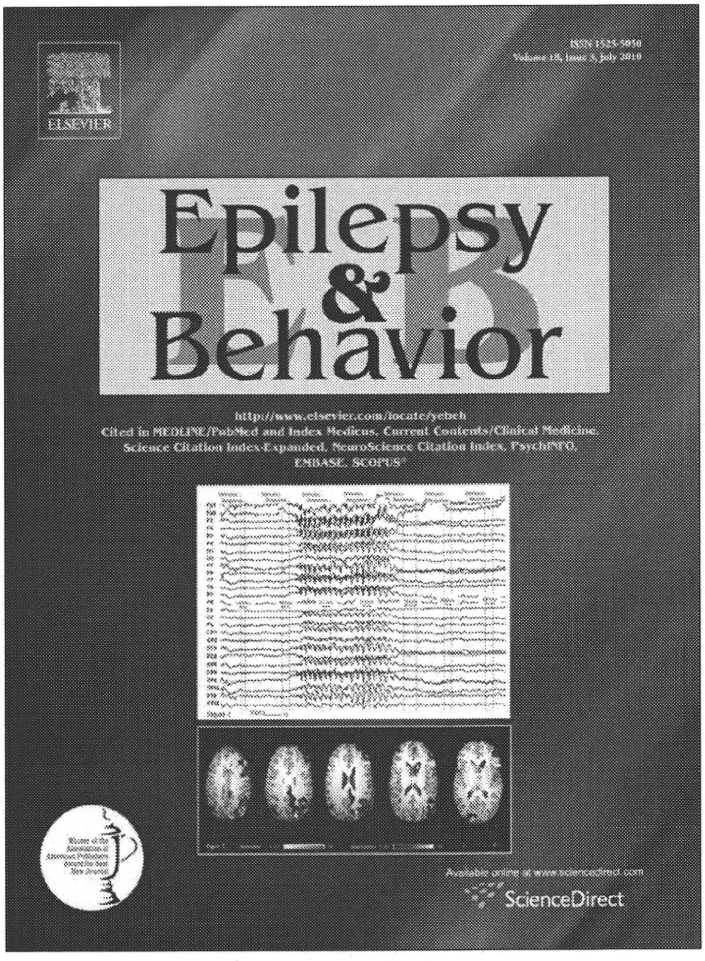

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Two forms of déjà vu experiences in patients with epilepsy

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ABSTRACT

Persons with epilepsy experience déjà vu phenomena with or without seizure recognition. Déjà vu experiences are also common mental phenomena in nonclinical individuals. The purpose of this study was to clarify two forms of déjà vu experiences in persons with epilepsy. Déjà vu experiences of 312 patients with epilepsy and 402 nonclinical individuals were evaluated using the Inventory of Déjà vu Experiences Assessment. In the patients with epilepsy, characteristics of déjà vu experiences with seizure recognition (SR form) were compared with those experiences with no seizure recognition (NSR form). The incidence (63.1%) of déjà vu experiences in patients with epilepsy was significantly lower than that (76.1%) of nonclinical individuals ($\chi^2 = 14.2$, $P = 0.000$). Among the patients with epilepsy, 55.6% had the NSR form and 24.0% had the SR form. Those with the NSR form manifested fewer psychopathological characteristics than did those with the SR form. Patients tended to view the SR form more negatively (i.e., frightened, uncomfortable, or disturbed) than the NSR form. The NSR form was significantly associated with idiopathic generalized epilepsies, less frequent antiepileptic drug administration, and no mesial temporal sclerosis. Although there was a significant association between the frequency of the SR form and patients' habitual seizures, the frequency of the NSR form was not associated with the frequency of the patients' habitual seizures. Persons with epilepsy experience two forms of déjà vu which are differently associated with their seizure recognition.

1. Introduction

Patients with epilepsy experience déjà vu as ictal phenomena either spontaneously [1,2] or artificially in response to electrical stimulation [3–5]. Gastaut [6] described epileptic illusions of déjà vu as ictal manifestations, resulting from discharge in the temporal cortex, during which previously unknown objects and situations, even though clearly perceived, appear familiar. Because déjà vu experiences have been classified as simple partial seizures [7], any déjà vu experiences of patients with epilepsy are likely to be regarded as epileptic phenomena.

Déjà vu experiences are also common mental phenomena in patients with nonepileptic neuropsychiatric diseases [8–10] or even in nonclinical individuals [11–13]. In recent community studies, approximately 70% of the nonclinical individuals reported some déjà vu experiences [14,15]. Patients with epilepsy can have nonepileptic subjective events as well as epileptic subjective events [16]. Although some authors have reported that déjà vu experiences occur more commonly during interictal periods than during seizures [17], no quantitative data have been presented. It is of interest whether patients with epilepsy experience various forms of déjà vu. Are some déjà vu experiences of patients with epilepsy similar to those of people without epilepsy?

The purpose of this study was to clarify whether patients with epilepsy experience different forms of déjà vu. As patients' recognition is an indispensable condition in the study of subjective mental experiences, such as psychic seizures, we investigated déjà vu experiences with or without the patients' seizure recognition.

2. Methods

2.1. Definitions

Déjà vu is defined as "any subjectively inappropriate impression of familiarity of a present experience with an undefined past" [18]. Déjà vu experiences as epileptic seizure phenomena are defined as simple

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partial seizures with psychic symptoms [7]. In the current study, déjà vu experiences recognized as habitual seizures by patients are classified as the seizure recognition (SR) form and those recognized as not related to seizure phenomena by patients are classified as the non-seizure recognition (NSR) form.

2.2. Participants

Three hundred twelve consecutive patients with epilepsy were recruited from six epilepsy outpatient clinics in Japan (Adachi Mental Clinic; National Centre Hospital for Mental, Nervous and Muscular Disorders; Tenshi Hospital; Nihon University Hospital; Aichi Medical University Hospital; and Musashino Kokubunji Clinic). To compare the prevalence of déjà vu experiences, we used 402 of the 479 nonclinical individuals who participated in our prior studies of déjà vu experiences [8,14,19,20]. These control subjects were matched with respect to age, sex, and education to the patients with epilepsy in the current study. These participants (i.e., users of community services or workers in private companies) had neither neurological nor psychiatric illnesses. All participants gave informed consent to participate in the study.

2.3. Research items

The following demographic features were evaluated in both the patients with epilepsy and the nonclinical individuals: age at the time of examination, sex, and total years of education. The patients with epilepsy were evaluated further to determine (1) age at onset of epilepsy; (2) duration of epilepsy; (3) epilepsy type (generalized epilepsy (GE) and partial epilepsy (PE) were diagnosed on the basis of seizure characteristics and clinical examinations in accordance with the international epilepsy classification [21]; PE was divided into temporal lobe epilepsy, frontal lobe epilepsy, parietal lobe epilepsy, and occipital lobe epilepsy); (4) frequency of seizures in accordance with the frequency guidelines previously reported [22]; (5) number of antiepileptic drugs (AEDs) taken; (6) lateralization of EEG abnormalities in interictal scalp EEG recordings [22]; (7) presence of mesial temporal sclerosis (MTS) detected by MRI according to our routine protocol and assessed qualitatively [23,24].

2.4. Assessment of déjà vu experiences

The Japanese version of the Inventory of Déjà vu Experiences Assessment (IDEA) [19,25] was used to assess déjà vu phenomena. All participants completed IDEA Part A (IDEA-A), which contains nine items and covers the frequency of déjà vu and its related psychobehavioral experiences (i.e., derealization, jamais vu, precognitive dreams, depersonalization, paranormal quality, remembering dreams, travel frequency, and daydreams). Although the IDEA is well standardized and validated in patients with epilepsy [19], we slightly modified it to specify the patient's seizure recognition. We conditioned on all of the IDEA-A items that the experiences occurred without the patient's seizure recognition. Furthermore, we added three items (items A10–A12, see Appendix A) to ask specifically about the SR form. Both patients with epilepsy and nonclinical individuals who experienced the NSR form (IDEA-A1) completed IDEA Part B (IDEA-B), which covers characteristics of the NSR form. Patients who had experienced the SR form (IDEA-A10) completed IDEA Part C (IDEA-C), which uses the same items from IDEA-B for the SR form. Test–retest reliability of the IDEA-A, -B, and -C items with the additional conditions and questions was evaluated and proven to be sufficient (n = 44, interval 3–6 months): IDEA-A (intraclass correlation coefficient [ICC] = 0.481–0.949, P = 0.000–0.017), IDEA-B (ICC = 0.493–0.886, kappa measure of agreement [κ] = 0.331–1.000, P = 0.000–0.169), and IDEA-C (ICC = 0.449–0.892, κ = 0.400–1.000, P = 0.000–0.166) (see Appendix A for details). Self-administered assessments were all conducted under clear consciousness with no distinct seizure activity for 12 hours or longer.

2.5. Analysis

For demographic data, one-way analysis of variance, χ^2 test, or Fisher's exact test was used. For the raw IDEA score data, differences and correlations were analyzed with the Mann–Whitney U test, χ^2 test, or Fisher's exact test. The Wilcoxon signed ranks test was used to analyze an individual's paired nonparametric variables. The relationship between each IDEA score and clinical factors was analyzed with the Spearman rank correlation coefficient. The binominal test or χ^2 goodness-of-fit test was used for comparisons of percentages. To test the reliability of the modified questionnaire, ICCs and κ values were used. A P value b 0.05 was considered significant. The Bonferroni correction was used for multiple comparisons when necessary. SPSS Version 14.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Characteristics of the study participants

Our population of patients with epilepsy comprised 164 men and 148 women, and the age at examination ranged from 17 to 66 years (mean = 34.7, SD = 10.9). Total years of education ranged from 9 to 19 (mean = 13.5, SD = 2.0). Age at onset of epilepsy ranged from 0 to 56 years (mean = 15.3, SD = 9.5). Duration of epilepsy ranged from 0 to 49 years (mean = 19.4, SD = 11.6). With respect to type of epilepsy, 49 patients had GE and 263 had PE. All of the patients with GE had idiopathic generalized epilepsy (IGE). Among the patients with PE, 143 had temporal lobe epilepsy (TLE), 79 had frontal lobe epilepsy (FLE), 16 had parietal lobe epilepsy {PLE), and 25 had occipital lobe epilepsy (OLE). Seizure frequency was classified as daily in 12 patients, weekly in 48 patients, monthly in 83 patients, yearly in 95 patients, less than yearly in 40 patients, and seizure freedom in 34 patients. The number of AEDs taken ranged from 0 to 5 (mean = 1.9, SD = 1.0). The main AEDs taken were carbamazepine in 186, valproic acid in 93, phenytoin in 110, phenobarbital in 78, zonisamide in 27, and benzodiazepines in 93 patients. EEG abnormalities were left-sided in 103, right-sided in 92, and bilateral in 109 patients, with no lateralization in 8 patients. MRI studies (n = 309) revealed left MTS in 29, right MTS in 20, and bilateral MTS in 10 patients, and were unremarkable in 250 patients.

The 402 nonclinical individuals comprised 199 men and 203 women and this distribution was similar to that of the patients ($\chi^2 = 0.66$, P = 0.451). Age at the time of examination ranged from 15 to 66 years (mean = 35.4, SD = 11.1), which was similar to that of the patients with epilepsy (F = 0.73, P = 0.393). Total years of education ranged from 9 to 18 (mean = 13.7, SD = 2.0), which was equivalent to that of the patients (F = 1.9, P = 0.173).

3.2. Frequency of the NSR and SR forms

In total, 197 (63.1%) of the 312 patients with epilepsy had some déjà vu experiences, whether NSR, SR, or both, a rate significantly lower than that of the nonclinical individuals (306/402, 76.1%) ($\chi^2 = 14.2$, P = 0.000). One hundred seventy-three (55.6%) had the NSR form, the frequency of which was significantly lower than that of the nonclinical individuals ($\chi^2 = 34.0$, P = 0.000). In addition, 75 (24.0%) had the SR form (IDEA-A10); the frequency of the SR form was weekly in 5 patients, monthly in 11 patients, yearly in 23 patients, and less than yearly in 20 patients; 16 patients had experienced the SR form previously but not within the last 3 years. Fifty-one (16.3%) patients had both NSR and SR forms.

3.3. Phenomenological differences between the NSR and SR forms

Among the 51 patients who had both NSR and SR forms, 43 (84.3%) felt there were some differences between the two forms according to their answers to IDEA-A12 (mean = 3.7, SD = 0.9, median = 4, n = 51). Phenomenological characteristics of the NSR form (as evaluated with IDEA-B, n = 309; two patients failed to answer) were compared with those of the SR form (IDEA-C, n = 75) (Table 1). Although the SR form occurred until recently and did so frequently at nighttime, the NSR form rarely occurred recently and showed no tendency of time of occurrence. The NSR form had significantly fewer psychopathological features (i.e., precognition, depersonalization, and derealization) than the SR form. Patients tended to view the SR form more negatively (i.e. frightened, uncomfortable or disturbed) than the NSR form. In addition, patients felt significantly more indifferent to or pleased about the NSR form than the SR form.

3.4. Relationship between NSR/SR forms and demographic characteristics

Age at examination was related significantly to frequency of the NSR form both in the patients with epilepsy ($r = -0.150$, $P = 0.008$) and in the nonclinical individuals ($r = -0.368$, $P = 0.000$). Frequency of the SR form in patients with epilepsy was not related to age at examination ($r = 0.054$, $P = 0.340$).There was no difference between the sexes in the frequency of the NSR form both in the patients with epilepsy ($z = -0.33$, $P = 0.744$) and in the nonclinical individuals ($z = -0.98$, $P = 0.329$). Sex was not related to the ictal form ($z = -0.14$, $P = 0.886$). Although duration of education was significantly related to the frequency of the NSR form in nonclinical individuals ($r = 0.116$ $P = 0.020$), such a relationship was not observed in the patients with epilepsy ($r = 0.008$, $P = 0.892$). The frequency of the SR form was related significantly to duration of education ($r = -0.150$, $P = 0.008$).

3.5. Relationship between NSR/SR forms and characteristics of epilepsy

Epilepsy characteristics relative to the NSR and SR forms are summarized in Table 2.

3.5.1. Age at onset of epilepsy and duration of illness

The frequency of the NSR form did not correlate with either age at onset or duration of epilepsy. In contrast, the frequency of the SR form correlated significantly with earlier age at onset of epilepsy and longer duration of epilepsy.

3.5.2. Epilepsy type

The NSR form occurred more frequently in patients with GE than in those with PE, whereas the SR form occurred more frequently in patients with PE than in those with GE. Among the patients with PE, the NSR form was observed in 68 of 143 (47.6%) with TLE, 46 of 79 (58.2%) with FLE, 10 of 16 (62.5%) with PLE, and 15 of 25 (60.0%) with OLE ($\chi^2 = 3.64$, $P = 0.304$). The SR form was observed in 45 (32.2%) with TLE, 18 (22.8%) with FLE, 2 (12.5%) with PLE, and 6 (24.0%) with OLE ($\chi^2 = 3.98$, $P = 0.268$).

3.5.3. Seizure frequency

The NSR form (median, less than yearly) occurred less frequently than did each individual's habitual seizures (median, yearly) ($z = -4.29$, $P = 0.000$). The frequency of the NSR form did not correlate significantly with the frequency of habitual seizures, whereas the frequency of the SR form correlated significantly with the frequency of seizures, particularly in those with partial seizures (complex partial seizures: $r = 0.219$, $P = 0.000$; simple partial seizures: $r = 0.275$, $P = 0.000$, $n = 263$).

3.5.4. Antiepileptic drug treatment

Patients with the NSR form took fewer AEDs (mean = 1.8, SD = 1.0) than those without the NSR form (mean = 2.1, SD = 1.0) ($F = 6.90$, $P = 0.009$), whereas patients with the SR form took a larger number of AEDs (mean = 2.1, SD = 1.0) than did those without (mean = 1.9, SD = 1.0) ($F = 3.86$, $P = 0.050$). Number of AEDs taken correlated significantly with the frequency of the NSR or SR form.

Table 1
Differences in phenomenologic characteristics between No Seizure Recognition (NSR)/ Seizure Recognition (SR) forms in epilepsy patients.

Nominal variables	NSR form (n = 171)	SR form (n = 75)	X^{2*}	P
B2-C1 Retrocognition			2.56	0.280
none	98	38		
vaguely	65	31		
clearly	8	6		
B3-C2 Elapsed period of time			28.6	0.000*
5 years or more ago	44	16		
1-5 years ago	52	17		
6 months-1 year ago	20	17		
2-6 months ago	15	3		
1-2 months ago	17	7		
1 month or less	23	15		
B4-C3 Duration			4.31	0.221
1 second or less	18	5		
seconds	115	47		
minutes	31	20		
hours	7	3		
B5-C4 Pervasiveness			5.62	0.060
totally	20	8		
partially	57	16		
/various	94	51		
B6-C5 Time of day			22.1	0.001*
no tendency	135	52		
daytime	27	10		
evening	6	9		
in bed	3	4		
B7-C6 Precognition			14.7	0.007*
none	127	48		
less than 1 year	31	13		
yearly	7	6		
monthly	4	6		
weekly	2	2		
B8-C7 Depersonalization			11.6	0.029*
non	125	44		
vague feeling it was not happening to me	13	9		
clear feeling it was not happening to me	2	2		
vague feeling I was looking at myself	20	16		
clear feeling I was looking at myself	11	4		
B9-C8 Repetition			3.54	0.469
exactly the same	11	2		
almost exactly the same	20	9		
the same	8	6		
approximately the same	25	12		
vaguely the same	107	46		
B10-C9 Derealization			11.6	0.023*
none	116	38		
a little unreal	21	9		
vaguely unreal	25	19		
unreal	6	5		
totally unreal	8	4		
B11-C10 Effects (yes/no)				
a. Indifference	75/96	16/59		0.000**
b. Alarm	28/143	34/41		0.000**
c. Reassurance	14/157	5/70		0.439
d. Pleasure	31/140	4/71		0.001**
e. Oppression	51/120	50/25		0.000**
f.. Surprise	76/95	25/50		0.039
g. Disturbance	38/133	35/40		0.000**

NSR form was assessed with the IDEA-B and SR form was assessed with the IDEA-C.
** With chi-squared goodness-of-fit test, **Binominal test with Bonferroni correction, 0.05/7 = 0.007**.*

Table 2
Relations between clinical characteristics and frequency of NSR/SR forms in epilepsy patients.

Variables	NSR form	SR form
Age of onset of epilepsy	R = -0.072/p = 0.208	R = -0.136/p = 0.017
Duration of epilepsy	R = -0.092/p = 0.103	R = 0.147/p = 0.009
Epilepsy type	GE 34/49 : PE 139/263	GE 4/49 : PE 71/263
	$X^2 = 4.57/p = 0.032$	$X^2 = 8.02/p = 0.005$
Seizure frequency	R = -0.064/p = 0.256	R = 0.286/p = 0.000
Number of antiepileptic drugs	R = -0.149/p = 0.009	R = 0.115/p = 0.043
Lateralization of EEG abnormalities	L 54/103 : R 47/92 : Bil 71/114	L 23/103 : R 29/92 : Bil 23/114
(n = 309)	$X^2 = 3.24/p = 0.137$	$X^2 = 3.88/p = 0.114$
MTS in MRI studies	Exist 26/59 : Nil 146/250	Exist 19/59 : Nil 56/250
(n = 309)	$X^2 = 3.97/p = 0.046$	$X^2 = 3.88/p = 0.143$

Spearman rank correlation coefficient (R), Chi-square test (X^2).
GE; generalized epilepsies, PE; partial epilepsies, L; left, R; right, Bil; bilateral, MTS; mesial temporal screlosis.

3.5.5. Lateralization of EEG abnormalities

Lateralization of EEG abnormalities was not significantly associated with frequency of the NSR and SR forms.

3.5.6. Mesial temporal sclerosis for MRI

Patients with MTS exhibited the NSR form less frequently than those without MTS, whereas there was no significant association between the SR form and MTS. The NSR form occurred in 10 (34.5%) of 29 patients with left MTS, 10 (50.0%) of 20 with right MTS, 6 (60.0%) of 10 with bilateral MTS, and 146 (58.4%) of 250 without MTS ($\chi^2 = 6.37$, P = 0.090). The SR form occurred in 7 (24.1%) with left MTS, 8 (40.0%) with right MTS, 4 (40%) with bilateral MTS, and 56 (22.4%) without MTS ($\chi^2 = 4.51$, P = 0.218).

4. Discussion

4.1. The distinction of déjà vu experiences

Our patients with epilepsy experienced different forms of déjà vu. The distinction of déjà vu experiences with patients' seizure recognition was validated by several findings. First, most of our patients differentiated with high reliability whether their déjà vu experiences were related to seizures or not. Their emotional responses to the two forms differed significantly. In general, patients' self-recognition of their habitual seizures is highly reliable [26]. Second, clinical characteristics (e.g., age at onset of epilepsy, epilepsy type, habitual seizure frequency, AEDs taken, and MTS) also differed between patients with the NSR form and those with the SR form. Third, the incidence of the NSR form (55.6% of all patients with epilepsy and 52.9% of those with PE) is much higher than expected for ictal phenomena, given that the reported incidence of all simple psychic seizures in patients with PE ranged between 10 and 25% [27–29]. Fourth, like déjà vu experiences in nonclinical individuals [15,30], the frequency of the NSR form decreased as age advanced, whereas the frequency of the SR form was not associated with age.

4.2. Frequency of the two forms of déjà vu in patients with epilepsy

Approximately 55% of patients with epilepsy were reported to have the NSR form, and this value is significantly lower than that for the nonclinical participants. Even when both the NSR and SR forms were considered, only 63.1% of the patients with epilepsy had experienced déjà vu. Although the reported incidence of déjà vu in patients with epilepsy ranges very widely from 23 to 85% [2,17,18,31], most studies have reported a lower incidence compared with that of the general population [15]. Interestingly, the frequency in our patients with epilepsy was similar to that of patients with other neuropsychiatric disorders [8,10]. Because ordinary déjà vu phenomena appear to develop as part of normal brain activity [14], patients with brain dysfunction may experience déjà vu less frequently.

4.3. NSR form and brain pathologies

The NSR form often occurred in patients without serious brain pathologies. Seventy percent of our patients with IGE had the NSR form, an incidence similar to that of the nonclinical individuals. In contrast, in our patients with PE (particularly those with MTS) the incidence of the NSR form was low, similar to that (42%) of patients with severe cerebral pathology [10]. Patients with IGE appear to have minor brain pathologies [32,33], whereas those with PE often have rather distinct cerebral pathologies [34]. Likewise, lower frequency of seizures, smaller number of AEDs taken, and absence of MTS were also associated with higher frequencies of déjà vu. These findings support the idea that the damaged brain generates the NSR form less frequently than the undamaged brain.

In the current study, patients with MTS experienced the NSR form infrequently. Patients with TLE had the lowest incidence of the NSR form among the patients with PE; however, this finding was not statistically significant. Although many studies have associated a network of temporal lobe structures with the SR form [1,3,34–36], there is no report of any focal brain lesion associated with the NSR form. Our present findings may indicate that undamaged temporal lobe structures play an essential role in generating the NSR form.

4.4. SR form and psychopathology

The SR form had more dissociative features, that is, depersonalization, derealization, and precognition, than did the NSR form. In general, déjà vu experiences in nonclinical individuals are rarely associated with pathological dissociations [20]. Our patients with epilepsy regarded the SR form as more unpleasant than the NSR form. This may be due in part to memories of subsequent serious seizure events. In addition, when patients with PE experience déjà vu ictally, the mesial temporal lobe structures may be involved with intense epileptic activity, and additional unpleasant sensations may be evoked.

4.5. Limitations

Several limitations of the current study should be considered. First, although the NSR form had many characteristics unrelated to severe epileptic conditions, it can still be considered a kind of unrecognized seizure. We have not confirmed the reported déjà vu experiences with EEG recordings or other examinations. There are considerable difficulties in capturing the NSR form with casual EEG recordings. Unlike frequent seizures in epilepsy surgery candidates, the NSR form occurs very infrequently; approximately 90% of the patients had these experiences yearly or less frequently. Even if these experiences could be captured, the NSR form would most likely produce no EEG changes. However, even the SR form can produce minimum EEG changes; 70–80% of independent simple psychic seizures yield unremarkable findings on intensive video/scalp EEG monitoring [37,38]. Second, although we used well-standardized assessment instruments, some subjective experiences could not be evaluated accurately. In particular, patients with epilepsy, when compared with nonclinical individuals, are likely to have memory dysfunction which can cause a specious reduction in such phenomena. Even in nonclinical individuals, the older the individual and the more advanced the decline in memory function, the less frequently déjà vu experiences are observed [14,15]. Subtle non-ictal phenomena may be dismissed more easily in comparison with intense ictal phenomena. Some patients may have forgotten their non-ictal experiences because of memory disturbances. However, whereas most non-ictal experiences

examined with the IDEA-A did not differ in frequency between patients and controls, it is unlikely that the patients dismissed or forgot only the déjà vu experiences. Nevertheless, further research on memory function and the NSR form is required. Third, as space was limited, we concentrated on clarification between the NSR and SR forms in patients with epilepsy and paid minor attention to the psychological characteristics of déjà vu experiences in patients with epilepsy and nonclinical individuals in this article. Psychological characteristics of these patients will be further analyzed in our next study.

In conclusion, patients with epilepsy could have two forms of déjà vu experiences (SR and NSR forms), although the NSR form was less common in patients with epilepsy than in nonclinical individuals. Despite several limitations, our results may contribute to the improvement of diagnostic reliability for patients with epilepsy with psychic experiences.

Conflict of interest statement

This study was done without any sponsorship. None of the authors report financial disclosures on this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yebeh.2010.02.016.

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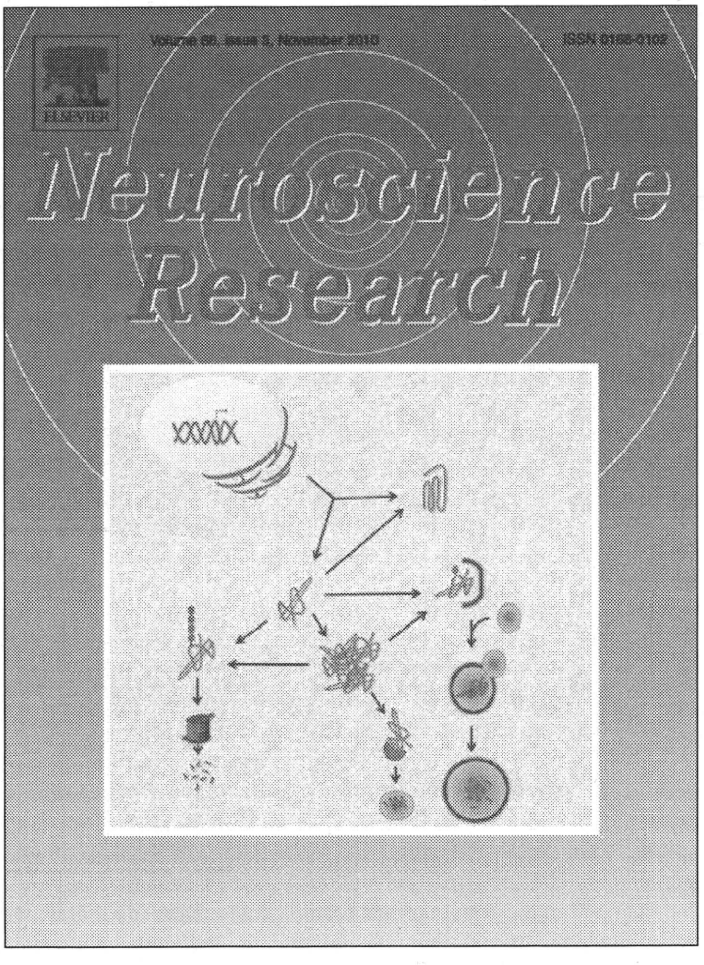

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Diurnal fluctuations in subjective sleep time in humans

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ABSTRACT

Humans have the ability to estimate the passage of time in the absence of external time cues. In this study, we subjected 22 healthy males (aged 21.8 ± 1.9 years) to a 40-min nap trial followed by 80 min of wakefulness repeated over 28 h, and investigated the relationship between various sleep parameters and the discrepancy (ΔST) of time estimation ability (TEA) during sleep, defined by the difference between actual sleep time (ST) and subjective sleep time (sub-ST) in each nap interval. Both ST and sub-ST were significant diurnal fluctuations with the peak in the early morning (9 h after dim-light melatonin onset time, 2 h after nadir time of core body temperature rhythm), and subjective sleep duration was estimated to be longer than actual times in all nap intervals (sub-ST > ST). There were significant diurnal fluctuations in discrepancy (sub-ST–ST) of TEA during sleep, and the degree of discrepancy correlated positively with increase in the amount of REM sleep and decrease in the amount of slow-wave sleep. These findings suggest that human TEA operates at a certain level of discrepancy during sleep, and that this discrepancy might be related to the biological clock and its associated sleep architecture.

1. Introduction

The human brain is endowed with the time estimation ability (TEA), making it possible to grasp the passage of time from milliseconds to hours without any specific time cues (Morell, 1996; Harrington et al., 1998; Lalonde and Hannequin, 1999; Rao et al., 2001; Ivry and Spencer, 2004; Tang and Harvey, 2005). TEA is believed to function during sleep as well as in waking hours (Hall, 1927; Brush, 1930; Omwake and Loranz, 1933; Lewis, 1969; Tart, 1970; Zung and Wilson, 1971; Bell, 1972; Moiseeva, 1975; Lavie et al., 1979; Hartocollis, 1980; Zepelin, 1986; Hawkins, 1989; Moorcroft et al., 1997; Born et al., 1999; Kaida et al., 2003; Aritake et al., 2004; Aritake-Okada et al., 2009). The notion that TEA operates in the brain even during sleep is supported by, for example, "self-awakening" whereby a person can wake up at a planned time without the use of a clock (Moorcroft et al., 1997) and "anticipated sleep termination" in which the adrenocorticotropic hormone (ACTH) level rises to coincide with the planned waking time (Born et al., 1999).

There is still much that remains unknown about the mechanism of TEA during sleep. In research to date, the success or failure of self-awakening has been related to psychological state (Omwake and Loranz, 1933; Hawkins, 1989), neuroendocrine activity (Born et al., 1999) and amount of physical activity (Lavie and Webb, 1975) before going to bed, and sleep architecture before waking (Kleitman, 1963; Tart, 1970; Zung and Wilson, 1971; Lavie et al., 1979; Zepelin, 1986; Aritake et al., 2004). Sleep architecture, in particular, has been related to amount of REM sleep (Lavie et al., 1979; Aritake et al., 2004) and slow-wave sleep (Aritake et al., 2004; Aritake-Okada et al., 2009) prior to waking. In studies by Aritake and colleagues (Aritake et al., 2004; Aritake-Okada et al., 2009), subjects were briefly woken once every 90 min (for six blocks of sleep in total) during a 9-h nighttime or 9-h daytime sleep period and were asked to give their subjective elapsed time, in an attempt to determine the effects of sleep depth and amount of sleep on TEA during sleep. This research found that irrespective of differences

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in sleep architecture between day and night sessions, subjective elapsed time during sleep was very close to actual sleep time, that subjective elapsed time was longer than actual sleep time in the first half of the 9-h sleep period (overestimate) but as sleep progressed, subjective elapsed time shortened, becoming shorter than actual sleep time in the second half of the entire sleep period (underestimate), and that subjective elapsed time was longer (accuracy decreased) the greater the proportion of slow-wave sleep (SWS) in a sleep block (Aritake-Okada et al., 2009). These results indicated that TEA operates even during sleep, and suggested that TEA could have a certain functional correlation with sleep architecture.

It is not clear what factors determine the discrepancy (between sub-ST and ST) of TEA during sleep, but it is possible that, in addition to sleep architecture, the circadian rhythm structure is involved (Campbell et al., 2001; Kuriyama et al., 2005; Spati et al., 2009). For example, Kuriyama et al. studied diurnal fluctuations in time perception during 30 h of sustained wakefulness, using a time production protocol in which subjects pressed a button to indicate a length of time they felt corresponded to a duration (10 s) presented in advance. Time production was found to be most accurate in the period from nighttime to morning, the descending phase in the core body temperature rhythm from its acrophase (Kuriyama et al., 2005). Campbell et al. (2001) asked subjects kept in isolation for 72 h to estimate the time when awoken, and showed that subjective elapsed time was most accurate in the ascending phase of the core body temperature rhythm from its nadir.

In the present study, we used an ultra-short schedule (short periods of sleep and wakefulness repeated over 24 h) to elucidate the characteristics of diurnal fluctuation in discrepancy of TEA and the relationship between discrepancy and sleep parameters. By dividing sleep into equal intervals throughout the day, the ultra-short schedule makes it possible to evaluate time estimation during sleep in various time periods over 1 day. To date, a number of ultra-short schedule protocols have been used to precisely study the relevance of various physiological parameters such as sleep structure and core body temperature rhythm (Lavie and Scherson, 1981; Lavie and Segal, 1989; Dijk et al., 1999; Buysse et al., 2005). For the present study, healthy subjects were entered into a 40–80 ultra-short schedule (repetition of a 40-min nap trial followed by 80 min of wakefulness) and asked immediately after each nap trial to estimate sleep time. This allowed us to characterize diurnal fluctuations in TEA during sleep to a high temporal resolution, and to extract sleep parameters related to discrepancy.

2. Methods

2.1. Participants

We recruited 22 healthy males (aged 21.8 ± 1.9 years) who kept regular hours. Subjects gave their written consent after a receiving a detailed explanation of the experiment. A doctor or psychiatrist interviewed the subjects to establish that they had no psychological or neurological disorders and had not taken any psychotropic drugs or other central nervous system agents. Subjects were asked to maintain their regular habits (recording their sleep–wake patterns on a sleep–wake rhythm chart) and to refrain from consuming caffeine, nicotine and alcohol from 1 week before the experiment. From 1 week before the experiment, all subjects wore a wristwatch-style activity monitor (Actiwatch-L, Mini-Mitter Co., Inc., Bend, OR, USA) and core body thermometer. Core body temperature was measured using the thermometer probe inserted into the rectum (model LT-8, Gram, Urawa, Japan) and was recorded on the portable logger every 2 min for 1 week. Sleep onset and waking times were confirmed using Actiware Sleep software to check that subjects were keeping regular hours leading up to study induction. Subjects agreed to keep the research objectives and study details secret to avoid information leakage and biasing of later subjects. This study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan.

2.2. Experimental procedures

The experiment was conducted over 2 days (Fig. 1). Subjects assembled in the laboratory at 12:00 h on experimental day 1. Throughout the experiment no time cues were given whatsoever. Between 12:00 h and 13:30 h electrodes were attached for measurement of EEG (C3–A2, C4–A1 and O1–A2, O2–A1), EOG (left-A2 and right-A1), chin EMG and ECG, according to the 10/20 international criteria. Subjects entered the 40–80 ultra-short schedule at 14:00 h on experimental day 1. In this schedule, 2 h constituted 1 block, with each block consisting of 80 min of enforced wakefulness in a reclining seat followed by a 40-min nap trial. An experimenter monitored each subject status via a CRT video monitoring system and was assigned to each subject to enforce wakefulness during the waking period. Polysomnographic (PSG) recording was carried out during the nap trial. Fourteen cycles of this 2-h block were repeated (28 h in total) until 18:00 h on experimental day 2. Subjects had

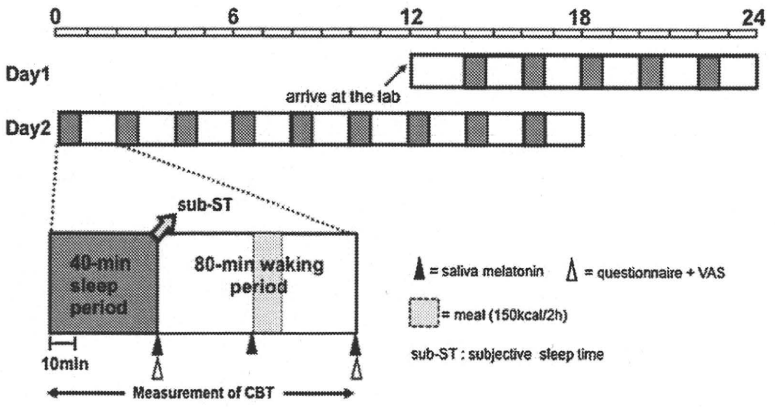

Fig. 1. The participants entered a 40–80 ultra-short sleep–wake schedule trial at 14:00 h on experimental day 1. This schedule consisted of 40-min nap trials followed by 80 min of wakefulness, with standard polysomnographic recordings being taken in bed in a dark (<0.1 lx), sound-attenuated room and the 80-min period of enforced wakefulness on a semi-upright sofa under room light conditions (150 lx). During the 80 min of wakefulness, participants were kept awake and monitored closely by experimenters. At the end of the nap trial, each participant was awoken gently. While remaining in a recumbent position, each participant answered the questionnaire and visual analoge scale (VAS) (□) regarding subjective passage of time and subjective sleep feeling, and thereafter left the bed. Participants were instructed to answer how much time they estimated had passed. Throughout the study, participants were given no information concerning the exact number and timing of the trials except that they would be alternating between nap trials and periods of enforced wakefulness. Following the repeated nap trials, saliva samples (▲) were taken during the 80-min period of wakefulness using saliva collection tubes.

been informed that they would follow a cycle of relatively short periods in and out of bed, but were not told the actual schedule. Illuminance in the laboratory was kept to 150 lx or below during wakefulness and 0 lx during sleep. Core body temperature was recorded every 2 min throughout the experimental period using a portable body temperature logger (resolution 0.02 °C; Vital Sense; Mini Mitter, USA). Throughout the experiment, room temperature (24.0 °C), humidity (60.0%), illuminance (≤150 lx during wakefulness, 0 lx during sleep), calorie and fluid intake (150 calorie snack and 200 ml drinking water every 2 h) and physical activity (seated and recumbent) were regulated.

2.3. Measures and analyses

2.3.1. Objective sleep evaluation

We analyzed PSG data from nap trials in the 12 blocks excluding the first one and last one blocks. Sleep stages were determined from PSG data during time in bed in 30-s epochs in accordance with the international criteria (Rechtschaffen and Kales, 1968). For each 40-min nap trial we obtained the recorded sleep time (ST) and time (min) and percentages of stage W stage 1, stage 2, stage 3 + 4 (SWS) and stage REM.

2.3.2. Subjective sleep evaluation

Subjects were gently roused at the end of the nap trial. While supine before getting out of bed, they were asked to give their subjective sleep time (sub-ST) and complete a questionnaire and visual analog scale (VAS) on items concerning their sleep state: specifically (1) subjective amount of sleep time (sub-ST; e.g. 30 min); (2) subjective sleep latency (e.g. 15 min); (3) subjective sleep depth (1: none, 2: a small amount, 3: a moderate amount, or 4: a lot); and (4) subjective alertness (assessed by the VAS). Subjects gave their sub-ST estimates from the lights-out time of each nap each trial; they were instructed to answer based on how long the elapsed time felt. Fluctuations in subjective parameters were then analyzed.

2.3.3. Discrepancy of TEA

The difference (ΔST) between sub-ST and ST was obtained, and this was defined as discrepancy of TEA (values closer to 0 indicate higher accuracy).

2.3.4. Core body temperature analysis

During the 28-h experiment, rectal temperature was recorded every 2 min and telemetric signals were stored on a computerized monitoring system (Vital Sense, resolution 0.02 °C, Mini-Mitter Co. Inc.) and then transferred to a PC. Smooth curve fitting was then carried out using Kaleidagraph (KaleidaGraph v4.0, Hulinks Inc., Tokyo, Japan). We describe temperature data obtained in the first and last 2-h periods. From the cosine curve, the time of the fitted minimum (nadir) and maximum (acrophase) were determined.

2.3.5. Melatonin analysis

Saliva samples for quantitation of saliva melatonin concentration were collected 80 min before, 40 min before and directly before a nap trial using a collection tube (Buhlmann Laboratories AG, Schonenbuch, Switzerland). Saliva samples were immediately refrigerated at −30 °C for lateranalysis. Saliva melatonin was measured with a highly specific direct double-antibody radioimmunoassay kit (Saliva Melatonin RIA kit, Buhlmann Laboratories AG) (Weber et al., 1997). The time point where the saliva melatonin level crossed 6.0 pg/mL was defined as the dim-light melatonin onset time (DLMO) (Lewy et al., 1999). In the assessment of DLMO, we also caluculated the relative threshold of 33% level crossing of the peak melatonin concentration in each subjects (Kawinska et al., 2005). There was a significantly higher correlation between the 33% level crossing and the 6.0 pg/ml level crossing ($r = 0.948$, $p < 0.0001$), and the level crossing 6.0 pg/ml was used as DLMO in our present study. DLMO was used for determining relative time (RT) for each subject as follows. The data series obtained from the 28-h experiment was time-locked to DLMO and was designated as RT21:00 for each subject. This designation was set based on the fact that in normal people DLMO occurs 14 h after waking time, typically around 21:00 h in clock time (Lewy et al., 1998). All time data are presented in 24-h format based on RT, and as such, we obtained standardized 28-h data for all the participants.

2.4. Statistical analyses

Comparison of variables obtained according to the time course were performed using one-way repeated measures ANOVA (within trial). Correlations were calculated using Pearsons coefficient. Statview version 5.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. The level of significance was set at $p < 0.05$. Values are expressed as mean ± standard error of mean (SEM).

3. Results

3.1. Diurnal fluctuations in objective parameters

One-way repeated measures ANOVA revealed significant fluctuations over time for sleep latency ($F(11, 231) = 27.938$, $p < 0.001$), ST ($F(11, 231) = 28.088$, $p < 0.001$), amount of SWS ($F(11, 231) = 2.355$, $p = 0.001$), amount of REM sleep ($F(11, 231) = 13.695$, $p < 0.001$), core body temperature ($F(11, 231) = 60.676$, $p < 0.001$), and melatonin secretion ($F(11, 231) = 38.207$, $p < 0.001$) (Fig. 2a–f).

The amplitudes of core body temperature and melatonin secretion rhythms were similar to a normal control group already described (Shibui et al., 2000), indicating that our subjects had normal biological timekeeping. The average DLMO clock time of our subjects was 22:57 h ± 98.4 (min). The nadir time of core body temperature was RT02:53, calculated using the cosinor method.

3.2. Diurnal fluctuations in subjective parameters

One-way repeated measures ANOVA revealed significant diurnal fluctuations in sub-ST ($F(11, 228) = 5.534$, $p < 0.001$); sub-ST was shortest at RT20:00, then lengthened to a maximum at RT06:00 (Fig. 3a). For other subjective parameters, one-way repeated measures ANOVA revealed significant fluctuations over time for subjective sleep latency ($F(11, 231) = 5.724$, $p < 0.001$), subjective depth of sleep ($F(11, 231) = 4.375$, $p < 0.001$), and subjective alertness ($F(11, 231) = 19.459$, $p < 0.001$) (Fig. 3b–d). Sub-ST and subjective depth of sleep were greatest between RT04:00 and RT06:00, exhibiting normal patterns which mirrored subjective sleep latency and subjective alertness (Dijk et al., 1999).

3.3. Discrepancy of TEA

Discrepancy of TEA, defined as ΔST, showed significant fluctuations over time ($F(11, 231) = 2.156$, $p = 0.017$) (Fig. 4a); ΔST was smallest (7.49 ± 8.49 min) at RT22:00, subsequently increasing to a maximum (34.29 ± 14.31) at RT06:00. At all measurement points ΔST was positive; the ratio of minimum to maximum was 4.58 (Fig. 4b).

3.4. Relationship between ΔST and sleep architecture

Sub-ST showed a significant positive correlation with ST ($r = 0.841$, $p = 0.001$) and %REM sleep ($r = 0.856$, $p = 0.001$), and a negative correlation with % non-REM (NREM) sleep ($r = -0.856$, $p = 0.001$), % stage 1 sleep ($r = -0.774$, $p = 0.002$), and % stage

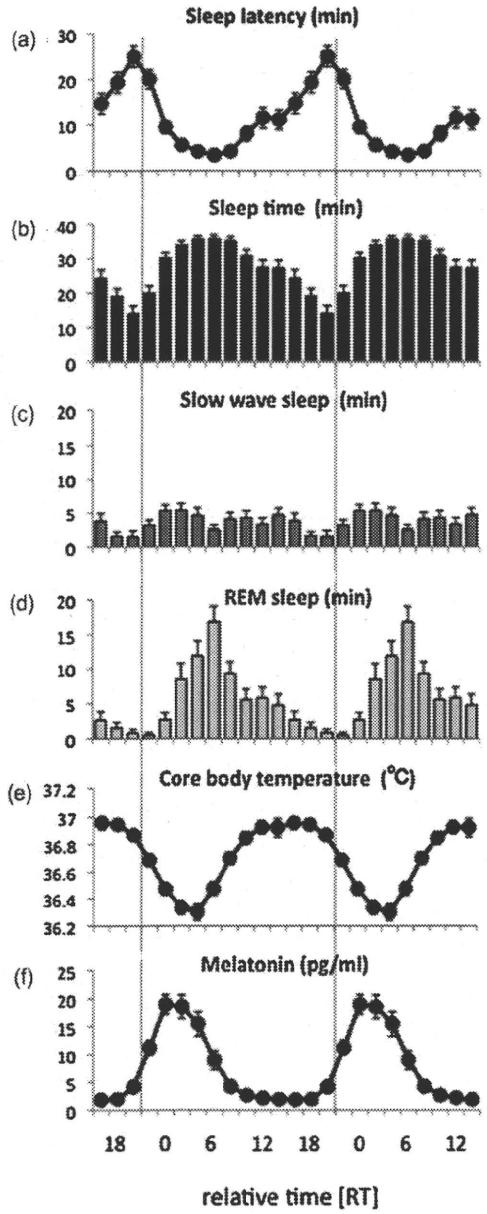

Fig. 2. Temporal fluctuations in the mean values of (a) sleep latency, (b) amount of sleep time, (c) amount of slow-wave sleep, (d) amount of REM sleep, (e) core body temperature, and (f) melatonin level. All data are depicted as double plots and time-locked to the onset of melatonin release at a relative clock time of 21:00 h.

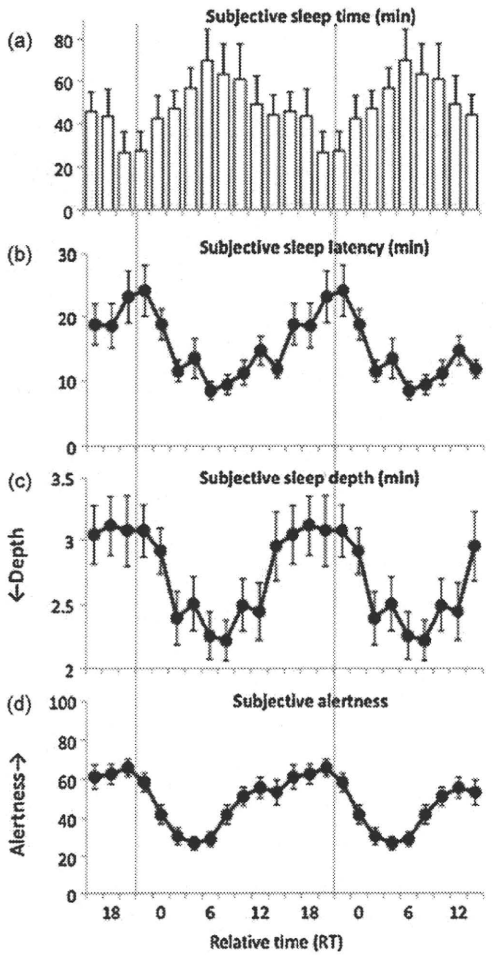

Fig. 3. Temporal fluctuations in the mean values of (a) subjective sleep time (sub-ST), (b) subjective sleep latency, (c) subjective sleep depth, and (d) subjective alertness. All data are depicted as double plots and time-locked to the onset of melatonin release at a relative clock time of 21:00 h.

2 sleep ($r=-0.742$, $p=0.004$). However, no significant correlation was noted between sub-ST and %SWS ($r=-0.362$, $p=0.256$). ΔST showed a significant positive correlation with %REM sleep ($r=0.664$, $p=0.02$) and significant negative correlations with % NREM sleep ($r=-0.664$, $p=0.02$) and %SWS ($r=-0.640$, $p=0.02$) (Fig. 5b, c, f). No significant correlation was noted between ΔST and ST ($r=0.479$, $p=0.118$), % stage 1 sleep ($r=-0.393$, $p=0.212$) or % stage 2 sleep ($r=-0.568$, $p=0.053$) (Fig. 5a, d, e).

4. Discussion

In this study we investigated the characteristics of diurnal fluctuations in TEA during sleep, and sleep parameters related to discrepancy of TEA, using a 40–80 ultra-short schedule of a 40-min nap trial followed by 80 min of enforced wakefulness repeated over 28 h. This method distributes sleep pressure by repeating short periods of sleep and wakefulness, allowing sleeping and waking parameters to be measured over a long period to a high temporal resolution while eliminating the accumulation of sleepiness and fatigue. Ours is the first study to use a 40–80 ultra-short schedule to evaluate the characteristics of diurnal fluctuations in TEA, which is believed to operate even during sleep. We found that the subjects in this study overestimated actual ST in all circadian rhythm phases. When investigating the factors governing discrepancy of perception of ST in relation to sleep architecture and regulation of biological rhythms, we discovered the following: (1) significant diurnal fluctuations in the extent of overestimation, or discrepancy of perception of ST (discrepancy between subjective ST and actual ST) and (2) significant correlations with sleep parameters in the sleep intervals.

Our subjects showed clear diurnal fluctuations in discrepancy of estimation of ST, with difference at its highest (largest ΔST) at RT06:00, this being 9 h after DLMO and about 2 h after the nadir of core body temperature rhythm. In this time period, the amount of REM sleep (%REM sleep) was also at its maximum, and there was thus a significant positive correlation between ΔST and %REM sleep. On the other hand, no significant correlation was seen between ΔST and ST. REM sleep time is governed by the biological clock, showing time-dependent diurnal fluctuations with a peak in the time period from early morning, when core body temperature is at its lowest, throughout the morning (Lavie and Scherson, 1981; Dijk et al., 1999; Buysse et al., 2005). This suggests that the

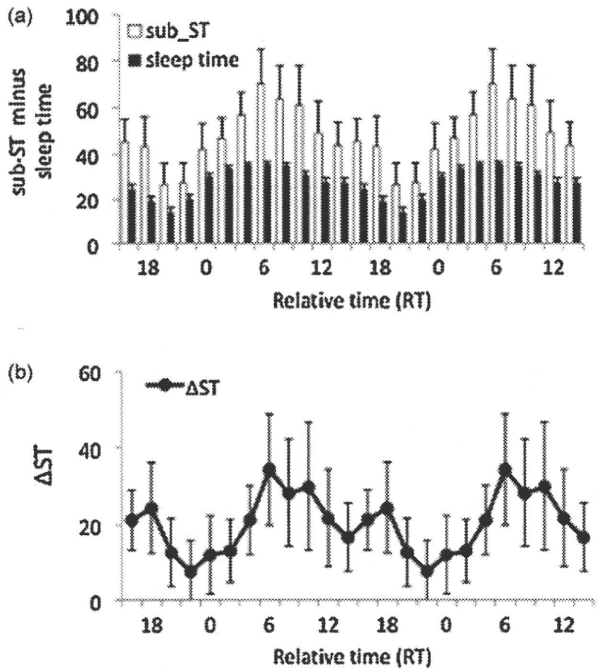

Fig. 4. (a) Difference between subjective sleep time duration (sub-ST) and sleep time (ST), which was obtained by actual sub-ST minus actual ST. (b) Discrepancy of sleep time estimation (ΔST).

discrepancy of TEA during sleep could be coupled to the biological clock through the temporal distribution of REM sleep time. It is not possible from this study to determine whether discrepancy in estimation of ST is directly governed by the biological clock or regulated through diurnal fluctuations in REM sleep time, but this question could perhaps be answered by carrying out shift experiments or intervention studies in which REM sleep time is regulated.

Before starting the experiment, we predicted that an increase in SWS, which induces a decrease in activity (decreased blood flow) in the prefrontal cortex (Maquet et al., 1997; Kajimura et al., 1999; Maquet, 2000), also would produce a increase in discrepancy of TEA during sleep. In recent years, research into brain regions responsible for time perception during wakefulness has revealed that, together with the basal ganglia (striatum) and cerebellum, activity in the prefrontal cortex plays a major role in time perception (Harrington et al., 1998; Lalonde and Hannequin, 1999; Ivry, 1996). In particular, it is thought that whereas the basal ganglia (striatum) and cerebellum are involved in time perception in millisecond units, the prefrontal cortex contributes to estimation of longer units in the order of minutes (Mangels et al., 1998; Lalonde and Hannequin, 1999). It has been reported that discrepancy in estimation of relatively long periods of time deteriorates when there is a decrease or disorder of activity in the prefrontal cortex (Mangels et al., 1998). We have also previously reported that ST tends to be overestimated (decreased accuracy) in the first half of natural sleep, when longer periods of slow-wave sleep occur (Aritake-Okada et al., 2009).

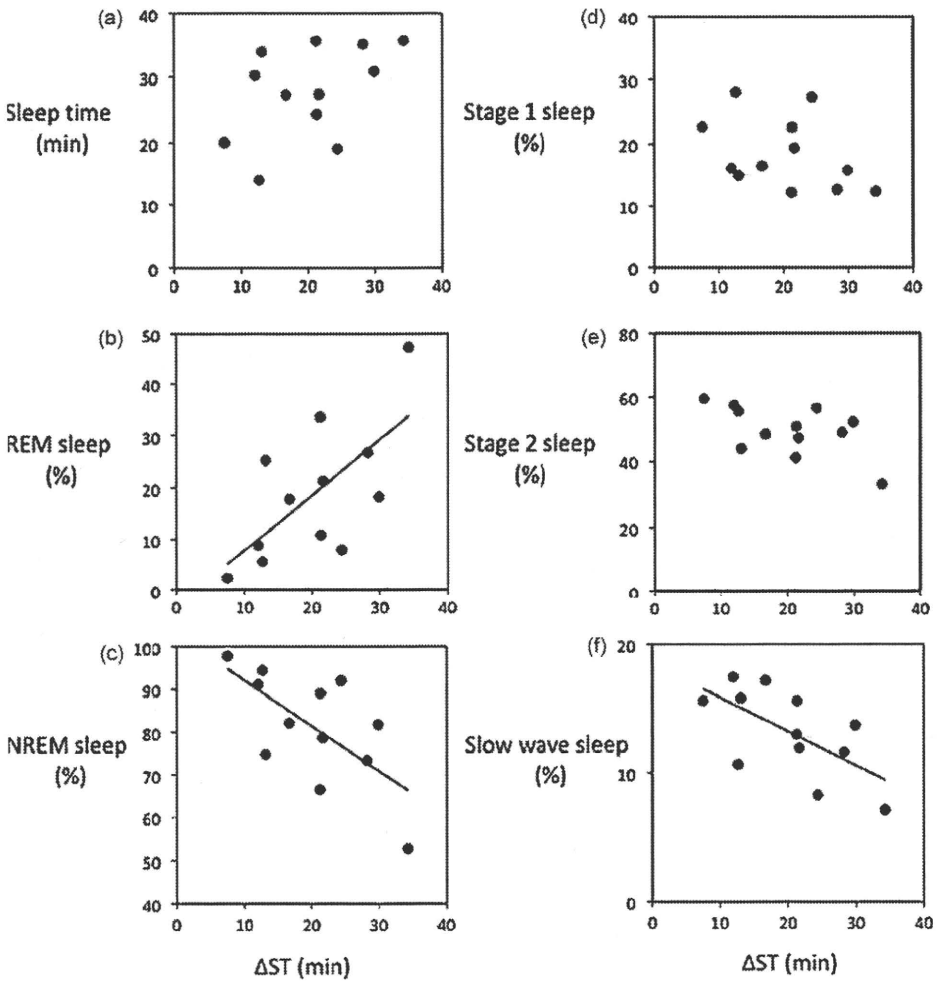

Fig. 5. Relationships between change in discrepancy of subjective sleep time (ΔST) and (a) sleep time (ST), and the percentages of sleep stages: (b) REM sleep, (c) non-REM (NREM) sleep, (d) stage 1 sleep, (e) stage 2 sleep, and (f) slow-wave sleep (f). ΔST was significantly correlated with the percentages of REM, NREM, and SWS sleep.

Contrary to our prediction, in the present study we saw a negative correlation between ΔST for nap intervals (40 min) and slow-wave sleep. We thus found that ΔST during sleep was in fact lower when there was more slow-wave sleep. It should be noted that in our study design, slow-wave sleep in the 12 nap intervals manifested for a maximum of about 5 min (5.37 ± 1.01 min on average) and there was very little variation between blocks (Fig. 2c). This level of slow-wave sleep is considerably smaller than in natural sleep, and we can assume it would have had a limited effect on cortical activity during sleep in any one block. It is therefore possible that the negative correlations seen between slow-wave sleep and ΔST, and NREM and ΔST, did not reflect a causal functional relationship between the two.

Conversely, we rather found positive relationship between ΔST and REM sleep. Although our study protocol does not allow separating the influence of the circadian timing system and REM sleep on subjective sleep time estimation, our result that a decrease in activity in prefrontal cortex during REM sleep (Maquet et al., 1996) could lead to deterioration of TEA during sleep. Maquet found that the decrease in cerebral blood flow (CBF) also during REM sleep (Maquet et al., 1996). In our study, REM sleep appeared for up to 16 min (16.86 ± 2.19 min on average) beyond SWS during 40 min nap trial. The REM sleep to this extent may affect the decrease in activity in prefrontal cortex followed by the discrepancy of TEA during sleep.

There are several points to consider when interpreting these results. Firstly, subjects may have learned through experience how long the sleep time was and this would have biased their estimates. In the experimental protocol for this study, subjects had to assess subjective ST without any time cues. It is, however, possible that over the 14 repeated cycles of the 40–80 ultra-short schedule subjects learned the length of nap time through experience. Nevertheless, there were clearly diurnal fluctuations in subjective ST and discrepancy of TEA over the sleep blocks, and the data appear to well reflect the physiological character of intrinsic regulatory mechanisms including sleep architecture and circadian rhythm structure. Secondly, we could not exclude the influence that the sleep stage directly before waking exerts on alertness and mood upon waking (Jewett et al., 1999). For this study we used a protocol in which subjects were forcibly woken after a fixed period (40 min) in bed with lights out, regardless of their sleep stage at that time. Therefore, in addition to the length of ST, we cannot rule out the possibility that the sleep stage upon being woken also influenced the evaluation of subjective sleep time. Research using a different design and a natural sleep setting would be needed to address this issue.

5. Conclusion

In this study we investigated biological rhythm and sleep architecture parameters in relation to discrepancy of TEA during sleep, using a 40–80 ultra-short schedule. Our findings offered ideas for exploring the as yet unelucidated physiological mechanisms of TEA during sleep. Disorders of time estimation are suspected to be involved in intractable insomnia, and there is a need to understand the mechanisms of this disease. Paradoxical insomnia (ICSD 2nd, 2005) is characterized by a marked underestimation of subjective ST relative to actual ST, and is in effect a discrepancy phenomena between sub-ST and ST (Salin-Pascual et al., 1992; Edinger and Fins, 1995; Perlis et al., 1997; Vanable et al., 2000; Edinger and Krystal, 2003). We believe that the results of this study will also contribute to an understanding of the disease mechanisms in such insomnia patients.

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