larly at a dose of 9×10^6 IU daily for the first 4 weeks and then three times per week for the following 20 weeks under an identical regimen of IFN-α treatment. Informed consent to perform the present study was obtained from all patients. The values for the serologic hepatic function of the 98 patients improved during IFN-α treatment. The means and standard deviations for the values of aspartate aminotransferase (AST/GOT) (normal: 8–38 IU/L) were 126.2 ± 75.1 IU/L before treatment, 50.7 ± 23.6 IU/L at 2 weeks of treatment, 43.2 ± 24.1 IU/L at 4 weeks of treatment, and 40.4 ± 23.1 IU/L after treatment. The values for alanine aminotransferase (ALT/GPT) (normal: 4–44 IU/L) were 164.1 ± 93.2 IU/L before treatment, 60.4 ± 33.2 IU/L at 2 weeks of treatment, 55.0 ± 29.1 IU/L at 4 weeks of treatment, and 52.4 ± 27.1 IU/L after treatment. No patient displayed elevation of serologic hepatic function during IFN-α treatment.

Quantitative-EEG Analysis

The EEG recordings and QEEG analysis used in the present study were described previously (Kamei et al., 1999). Briefly, serial EEGs were obtained before IFN-α treatment, at 2 and 4 weeks of treatment, and at 2 to 3 days after the treatment. The serial EEGs at 2 and 4 weeks of treatment were examined during the period from 1 to 6 hours after the injection of IFN-α. The EEGs in each subject were recorded on a magnetic optical disk from 16 electrode locations according to the international 10–20 system using a digital EEG instrument (Neurofax EEG-4518; Nihon Kohden, Tokyo, Japan). The EEGs were referenced to the ipsilateral earlobes. Sixty seconds of QEEG data were selected visually from each subject and digitized at 128 Hz with a time constant of 0.3 by using a high-frequency filter of 60 Hz. Thirty epochs with a duration of 2 seconds were collected from the subsequent resting period during which time the subjects'eyes were closed for QEEG analysis. The analytical procedure involved the application of fast-Fourier transformation of the collected EEG signals by Rhythm 10.0 (Stellate Systems Inc, Montreal, Quebec, Canada). The frequency ranges were divided into six bands: delta (1.17–3.91 Hz), theta 1 (4.30–5.86 Hz), theta 2 (6.25–7.81 Hz), alpha 1 (8.20–10.16 Hz), alpha 2 (10.55–12.89 Hz), and beta (13.28–30.86 Hz). The absolute powers of each frequency band were calculated at each electrode location in each subject. Each power value was obtained by integrating the appropriate part of the spectrum. The present quantitative analysis was carried out blindly during routine EEG work involving many other disease states, including epilepsy, cerebrovascular disease, encephalitis, meningitis, metabolic encephalopathy, and brain tumor, as well as in normal controls. The only knowledge that the EEG analyst (S.K.) possessed regarding each patient was the his or her identification number, and he did not therefore have any other information concerning any of the studied subjects such as their clinical diagnosis, date of treatment, or kind of treatment.

Statistical Analysis

In June 2004, the statistical analyst (K.H.) collected the QEEG-analyzed data for the 98 subjects and information about the ages of the patients at another independent institute. The patients'ages were classified into five groups: 20 to 29, 30 to 39, 40 to 49, 50 to 59, and ≥60 years. The distributions of the power values at each frequency band for each electrode location were evaluated in terms of their skewness and kurtosis. According to the data obtained for the skewness and kurtosis, repeated-measure analysis of variance (ANOVA) was applied to the alterations in power values as the main factor among four different periods: before the IFN-α treatment, at 2 and at 4 weeks of treatment, and after the treatment, with the frequency bands, electrode locations, and patients'age classifications as cofactors. the statistical software StatView 5 (Abacus Concepts, Berkeley, CA, U.S.A.) was used. The QEEG variables were evaluated in relation to patient age by post hoc analysis of variance (Scheffé test). Probability values of less than 0.05 were considered as significant.

RESULTS

The 98 subjects ranged in age from 23 to 70 years (mean ± SD: 47.9 ± 10.6 years). The results of the serial QEEG studies for each selected frequency of EEG during the IFN-α treatment in each age group are summarized in Fig. 1. Increased slow waves (delta, theta 1 and 2) and decreased alpha 2 and beta waves were evident during the IFN-α treatment in all age groups. Such EEG alterations during the IFN-α treatment in the present blind, prospective, multicenter controlled study confirmed our previous observations (Kamei et al., 1999). Moreover, the alterations in power values during the IFN-α treatment became more remarkable as the patients'age increased. Statistical data for the analysis of the alterations in power values and ages obtained by the repeated-measure ANOVAs and post hoc ANOVAs are presented in Tables 1 and 2. The repeated-measure ANOVA results for the alterations in power values revealed a significant difference between the alteration in power values during the treatment and either the patients'age or frequency band (both $P < 0.0001$). The post hoc ANOVA results indicated that there were significant differences in the alterations of absolute power values during the IFN-α treatment for all comparisons with increasing patient ages in the case of the delta, theta 1, and beta waves, except for several comparisons with only 10-year alterations of age group. There were no significant differences in the alterations of power values during the IFN-α treatment in the case of the alpha 1 and total power values.

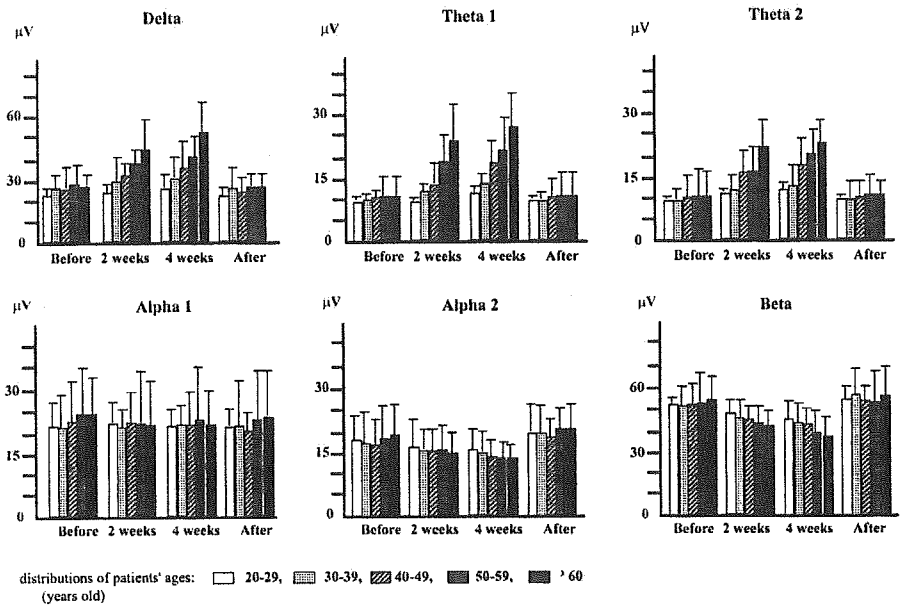

FIGURE 1. Alterations in absolute power values (mean ± SD) with changes of patients'age for each frequency band at before IFN-α treatment, at 2 and at 4 weeks after treatment, and at 2 to 3 days after treatment. Increasing power values in the slow waves (delta, theta 1 and 2) and decreasing power values in the alpha 2 and beta waves during IFN-α treatment, in comparison with those observed before and after IFN-α treatment, were evident for all age classifications. Moreover, the alterations in power values became more remarkable with increasing age in all frequency bands except for the alpha 1 and total power values.

TABLE 1. Repeated-measure Analysis of Variances Between Alterations in Power Values During IFN-α Treatment and Patient Age

Factors	
Alteration of power values during IFN-α treatment (Alteration of power values)	$P < 0.0001$ ($F = 30.338$)
Alteration of power values × Difference of patients' ages (Difference of age)	$P < 0.0001$ ($F = 16.081$)
Alteration of power values × Frequency bands	$P < 0.0001$ ($F = 48.781$)
Alteration of power values × Electrode location	NS
Alteration of power values × Difference of age × Frequency bands × Electrode location	NS

NS, not significant; x, interaction.

DISCUSSION

Although many patients have undergone IFN-α treatment, controlled detailed assessments of the adverse effects of IFN-α on the function of the central nervous system have not yet been described. Evaluations of brain functional alterations have been given in only three previous reports based on data from small numbers of patients who received EEG examinations (Meyers et al., 1991; Rohatiner et al., 1983; Smedley et al., 1983). We recently confirmed a significant, diffuse slowing on QEEGs that occurred in chronic hepatitis C patients during IFN-α treatment at a relatively low dosage (Kamei et al., 1999). At such a low dosage of IFN-α administration to chronic hepatitis C patients, the diffuse slowing of the EEG is reversible after completion of the treatment (Kamei et al., 1999). However, in one previous case report involving a high dosage of IFN-α, the alteration in the EEG was found to be persistent (Meyers et al., 1991). Moreover, neuropsychiatric complications have been described as difficult to evaluate after IFN-α treatment in patients with chronic viral hepatitis (Saracco and Rizzetto, 1999). In view of the considerable numbers of patients undergoing IFN-α treatment, detailed knowledge of the factors that influence EEG alterations due to IFN-α treatment is important for practicing physicians to predict the appearance of such adverse effects on brain function after IFN-α treatment. The results obtained in present study indicate that patient age is one of the factors that influence the alteration in EEGs during IFN-α treatment. Serial monitoring by EEG is thus considered to be of value for detecting alterations of brain function during IFN-α treatment in chronic viral hepatitis patients, and the alterations in the serial EEGs should be monitored carefully, particularly in older patients.

CONCLUSION

We evaluated the correlation between QEEG alterations that occurred during IFN-α treatment and the age of patients with chronic hepatitis C. A total of 98 patients with chronic hepatitis C underwent blind, prospective, and serial

TABLE 2. Statistical Comparisons of Alterations in Power Values During IFN-α Treatment for Each Frequency Band Among Each of the Patient's Age Distributions, by Post Hoc ANOVAs

Comparison of Different Age Distributions	Power Values (μV)						
	Delta	Theta 1	Theta 2	Alpha 1	Alpha 2	Beta	Total
G2 vs. G3	*	†	NS	NS	NS	†	NS
G2 vs. G4	*	*	*	NS	†	*	NS
G2 vs. G5	*	*	*	NS	*	*	NS
G2 vs. G6	*	*	*	NS	*	*	NS
G3 vs. G4	†	†	†	NS	NS	NS	NS
G3 vs. G5	*	*	*	NS	†	†	NS
G3 vs. G6	*	*	*	NS	†	*	NS
G4 vs. G5	*	*	†	NS	NS	†	NS
G4 vs. G6	*	*	*	NS	†	*	NS
G5 vs. G6	*	*	*	NS	NS	†	NS

Distributions of patients' ages (years old): G2 = 20–29, G3 = 30–39, G4 = 40–49, G5 = 50–59, G6 ≥ 60.
*$P < .01$.
†$P < .05$.
NS, not significant.

QEEG examinations at three independent hospitals. Our results show that the EEG alterations observed during IFN-α treatment in patients with chronic hepatitis C became more remarkable as the age of the patients increased.

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Never-treated patients with schizophrenia in the developing country of Bali

Toshiyuki Kurihara [a,*], Motoichiro Kato [b], Robert Reverger [c], I Gusti Rai Tirta [d], Haruo Kashima [b]

[a] *Komagino Hospital, 273 Uratakao, Hachioji, Tokyo, 193-8505, Japan*
[b] *Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan*
[c] *Wangaya General Hospital, Bali, Indonesia*
[d] *Bangli Mental Hospital, Bali, Indonesia*

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Abstract

Background: A considerable number of individuals with schizophrenia go undiagnosed and untreated in developing countries. In the current study, we investigated the prevalence of schizophrenia, the treatment status of individuals with schizophrenia, and factors associated with never-treated status in a Balinese rural community.
Method: A door-to-door survey was conducted on 8546 people from the general population to detect individuals with schizophrenia using standardized screening instruments in Bali.
Results: Thirty-nine individuals with schizophrenia were identified, giving a point prevalence of 4.2 per 1000 population. Never-treated group subjects ($n=20$: 51.3%) had a significantly higher total score on the Positive and Negative Syndrome Scale ($p<0.05$) and were less likely to have a history of violent behavior ($p<0.01$) than Treated group subjects ($n=19$: 48.7%). All 9 subjects who had never shown violent behavior remained untreated.
Conclusion: The clinical condition of the never-treated individuals with schizophrenia was poor. Individuals with schizophrenia without violent behavior had no opportunity to undergo medical treatment in this developing country setting.

Keywords: Schizophrenia; Developing countries; Community psychiatry; Epidemiology; Violent behavior

1. Introduction

Little is known about the current status of schizophrenic patients in developing countries due to the limited number of community-based studies. Schizophrenia has been regarded as less common in traditional societies than in nontraditional societies;

* Corresponding author. Tel.: +81 426 63 2222; fax: +81 426 63 3286.
E-mail address: kurihara@sj8.so-net.ne.jp (T. Kurihara).

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however, this rather old insight is still controversial (Allen, 1997). Furthermore, it is unclear to what extent individuals with schizophrenia remain untreated and the reason why they do so in developing countries. Violent behavior may be a common factor leading schizophrenic patients to initiate psychiatric treatment anywhere; however, Volavka et al. (1997) reported that the occurrence rate of assault with their first-in-lifetime contact with a helping agency was three times higher in developing than in developed countries. How can this finding be explained within the cultural context of developing countries? This community-based study investigates the prevalence of schizophrenia, the treatment status of individuals with schizophrenia, and factors associated with never-treated status in a Balinese rural community.

2. Method

2.1. Background

Bali is located in Southeast Asia and is one of more than 10,000 islands that make up Indonesia. It is famous as a tourist resort and for its unique Hindu-based culture. There are 3,048,317 people living in Bali (2001) and the island is almost entirely ethnically and culturally homogeneous. The industry is now in the developing stages. The basic unit of society is a community referred to as "banjar", which consists of several hundred households. Both the religious ceremonial aspect and social activity of the *banjar* is recognized as essential in Bali. Bali has 260 psychiatric beds, of which 225 are at the Bangli Mental Hospital, the primary mental health facility on the island, with a further 25 at a private mental hospital and 10 at a general hospital.

2.2. Sampling method

A door-to-door survey was conducted to detect individuals with schizophrenia who fulfilled the criteria of DSM-III-R (American Psychiatric Association, 1987) at 9 randomly and consecutively selected *banjars*. The demographic data of each community are shown in Table 1. The names of the *banjars* are disguised to protect the patients' privacy. In Bali, there is one urban center in the capital city of Denpasar, but all of the communities selected for this study were located in rural areas, which predominate in Bali. The first author obtained the cooperation beforehand of central and local governments for the study, as well as that of the head of each community. Thus, all of the 1966 households with 8546 residents in the selected communities participated with the case detection of schizophrenia.

2.3. Interview for case identification

The first author (TK), a psychiatrist who speaks Indonesian and Japanese, performed a face-to-face family interview with one family member as a key informant for each of the 1966 households with 8546 residents between June 2001 and July 2002. The targeted age was above 15, thus 6038 of 8546 residents were selected as subjects for case detection. FH-RDC (Family History-Research Diagnostic Criteria) (Endicott et al., 1978) was used to detect possible

Table 1
Prevalence data in each community

	Number of households	Number of people (male/female)	Number of people+15 y.o. (male/female)	Number of individuals with schizophrenia identified (male/female)
Community A	218	918 (478/440)	661 (344/317)	6 (3/3)
Community B	242	1096 (545/551)	779 (382/397)	2 (1/1)
Community C	70	343 (152/191)	216 (96/120)	2 (1/1)
Community D	195	845 (424/421)	613 (310/303)	2 (2/0)
Community E	113	564 (276/288)	439 (217/222)	2 (1/1)
Community F	318	1330 (683/647)	925 (472/453)	3 (0/3)
Community G	277	1228 (585/643)	841 (396/445)	7 (7/0)
Community H	360	1443 (698/745)	1010 (484/526)	6 (3/3)
Community I	173	779 (391/388)	554 (281/273)	9 (7/2)
Total	1966	8546 (4232/4314)	6038 (2982/3056)	39 (25/14)

cases that fulfilled the criteria either of schizophrenia or schizophreniform disorder classified in the DSM-III-R. For the suspected cases, the first author conducted a direct interview using SCID (Structured Clinical Interview for DSM-III-R) (Spitzer et al., 1990) NP version to examine whether the cases actually fulfilled the DSM-III-R criteria of schizophrenia or schizophreniform disorder. During this diagnostic procedure, the first author was blind to the subject's history of psychiatric medical treatment. The first author stayed in Bali exclusively for psychiatric research purposes. Interviews were performed either at the interviewee's home, or at a meeting place in the community, to limit the amount of time expended for a home visit.

2.4. Screened subjects

Thirty-six residents were diagnosed as having schizophrenia and 3 as having schizophreniform disorder. All 3 residents diagnosed as having schizophreniform disorder were rediagnosed as having schizophrenia 6 months after their onset of illness. Thus, 39 individuals with schizophrenia were screened, and these people are the subjects for the present study.

2.5. Reliability of the diagnosis

The reliability of the diagnosis of schizophrenia by the first author was established (Kurihara et al., 2002). To examine false negatives on the FH-RDC, the first author directly interviewed 300 randomly selected residents who were not suspected to have schizophrenia or schizophreniform disorder in the randomly selected community (community I). Consequently, neither patients with schizophrenia nor schizophreniform disorder were found; thus, no false negatives were found in the survey in community I.

2.6. Interview for screened subjects

A subsequent interview for screened subjects was also performed by the first author. At least two key relatives who played a central role in caring for the patients were selected. The interview was performed for 39 schizophrenic subjects and their key relatives. The clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay and Opler, 1987). The validity and reliability of the Indonesian version has also been established (Salan et al., 1994). Eguma's Social Adjustment Scale (ESAS) (Eguma, 1962; Ogawa et al., 1987) was used for the assessment of social adjustment. The ESAS has five categories: (A) Self-supportive, (B) Semi-self-supportive, (C) Socially adjusted to family or community, (D) Maladjusted, and (E) Hospitalized. On the ESAS, we developed a point-scoring system from 1 to 5 to quantify the range from A to E for statistical analysis. The reliability of the clinical interview carried out by the first author in Bali was established (Kurihara et al., 2002). Moreover, the past history of violent behavior of the subjects was examined in detail. An originally developed semi-structured interview based on a standard form was conducted to determine if the subject had a history of violent behavior. In brief, the definition of violent behavior used in the present study included battery, threats or hazardous acts with a weapon in hand, and damage to property. Violent behavior, which is strictly prohibited and very rare in Balinese communities, is not easily forgotten by family members. Nonetheless, the first author asked at least two key relatives about whether the patient had a history of violent behavior to reduce the risk of memory bias. After these assessments and interviews, the first author asked the subjects and their key relatives detailed questions regarding past history of and present status of psychiatric medical treatment. Both the type and duration of treatment were reconfirmed using medical records. For treated subjects with a history of violent behavior, whether the behavior occurred before medical treatment was determined.

In the present study, treatment was defined as antipsychotic medical treatment; thus, treatment by native healers was not taken into account when subjects were divided into a Treated group and Never-treated group.

3. Results

3.1. Prevalence of schizophrenia

Of 8546 individuals, including 6038 potential subjects over 15 years of age, 39 schizophrenic patients were detected. Excluding the 3 patients diagnosed with schizophreniform disorder at the screening but whose diagnosis was subsequently changed to schizophrenia, a point prevalence was found for schizophrenia of 4.2 per 1000 people

Table 2
Socio-demographic data between the two groups

	Treated group ($n=19$)	Never-treated group ($n=20$)
Sex (male/female)	14/5	11/9
Age	38.6 (11.9)	38.7 (16.9)
Educational period	5.4 years (4.0)	3.6 years (3.3)
Family history of psychosis (present/absent)	7/12	12/8
Number of family members	6.9(2.8)	6.4 (4.0)
Marital status (single/married/ divorced or widowed)	7/11/1	11/5/4

Chi-squared test was performed for sex, family history of psychosis, and marital status.
Two tailed t-tests were conducted for the other 3 items. ( ) SD.

from the general population and 6.0 per 1000 people from the population at risk in terms of age (i.e., over 15 years old).

3.2. Subject's socio-demographic data

Of the 39 subjects, 25 were males and 14 were females. The subjects had a mean age of 38.7 yr (SD14.46), mean educational period of 4.4 yr (SD3.75), and mean number of family members in the same compound of 6.6 (SD3.41). Sixteen subjects were married, 18 were single, 4 were divorced, and one was widowed.

3.3. Subject's clinical data

The subjects had a mean age at onset of 24.1 yr (SD 7.49) and mean duration of illness of 14.9 yr (SD 12.1). Of the 39 subjects, 19 (48.7%) had received psychiatric medical treatment at some point after their onset of illness, whereas 20 (51.3%) had not undergone any psychiatric treatment in the past. Of 19 treated subjects, 2 (5.1%) had been on medication regularly, whereas the remaining 17 subjects (43.6%) had been on irregular and/or brief medication over the course of their illness. Moreover, of 19 treated subjects, 12 had been admitted to a mental hospital, their mean number of admissions was 2.1, and the mean overall duration of admission was 96.7 days. In contrast to medical treatment, all the subjects had undergone traditional healing.

The mean positive, negative, general psychopathology, and total scores on the PANSS were 19.41 (SD7.19), 20.44 (SD9.36), 39.03 (SD12.10) and 78.87 (SD25.43), respectively. Twelve subjects (30.8%) were classified on the ESAS as "self-supportive", 6 (15.4%) as "semi-self-supportive", 10 (25.6%) as "socially adjusted to family or community", 11 (28.2%) as "maladjusted", while none were classified as "hospitalized". Thirty (76.9%) had a history of violent behavior. Between the subjects who had shown violent behavior in the past and non-violent subjects, no significant difference was found either in the PANSS or ESAS scores.

3.4. Comparison of socio-demographic data between treated group and never-treated group

The socio-demographic data of the Treated group ($n=19$) and the Never-treated group ($n=20$) are shown in Table 2. No significant difference was found in sex, age, educational period, family history of psychosis, number of family members, or marital history between the two groups.

3.5. Comparison of clinical data between treated group and never-treated group

The clinical data of the Treated group and Never-treated group is shown in Table 3. No significant difference was found in age at onset, duration of illness, or ESAS score between the two groups.

The total score of the PANSS was significantly higher in the Never-treated group than in the Treated group ($p<0.05$: two tailed t-test). As for the subscale of the PANSS, the general psychopathology subscale score was significantly higher in the Never-treated group than in the Treated group ($p<0.05$: two tailed t-test). Moreover, both the positive and negative subscale scores also tended to be higher in the Never-treated group; however, it did not reach the level of a statistically significant difference. The subjects in the Treated group had a significantly greater history of violent behavior than those in the Never-treated group ($p<0.01$: Chi-square analysis). All 9 subjects who had never shown

Table 3
Clinical data between the two groups

	Treated group ($n=19$)	Never-treated group ($n=20$)
Age at onset	25.1 (8.2)	23.1 (6.8)
Duration of illness	14.2 years (11.7)	15.7 years (12.7)
PANSS scores		
Positive subscale	18.16 (8.78)	20.60 (5.21)
Negative subscale	18.05 (8.50)	22.70 (9.78)
General psychopathology subscale	34.47 (9.68)*	43.35 (12.80)
Total score	70.68 (23.78)*	86.65 (25.03)
Eguma's Social Adjustment Scale	2.37 (1.21)	2.65 (1.23)
History of violence present/absent	19/0**	11/9

Chi-squared test was performed for history of violence.
Two tailed t-tests were conducted for all other items; *$p<0.05$; **$p<0.01$; ( ) SD.

violent behavior remained untreated, whereas all of the treated subjects showed violent behavior in the past. Information, both from medical records and family interviews revealed that violent behavior among treated subjects occurred at least once within a month before medical treatment in all cases, and aggressiveness was observed in all of these subjects at the time of first contact with psychiatric care.

4. Discussion

For over a century, one of the most essential questions of epidemiological research into schizophrenia is what is the true population frequency of the disorder and how is it distributed across and within various population groups (Jablensky, 2000). Data on whether the prevalence of schizophrenia is the same across cultures remain inconclusive, with some epidemiological studies from developing countries reporting a low prevalence (Kulhara and Chakrabarti, 2001). In the present study, a point prevalence was found for schizophrenia of 4.2 per 1000 people from the general population and 6.0 per 1000 people from the population at risk in terms of age (i.e., over 15 years old). According to a review of epidemiological studies by Jablensky (2000), the majority have produced prevalence estimates in the range of 1.4–4.6 per 1000 population at risk, though certain populations and groups deviate from the central tendency. Reviewing epidemiological studies, Goldner et al. (2002) revealed that the best estimate rates of schizophrenia for 1-year prevalence are 3.4 per 1000 population. Thus, the point prevalence of the present study is higher than the prevalence estimates of both Jablensky and Goldner. Our finding contributes epidemiological data to the literature suggesting that schizophrenia is not less common in developing countries, at least in Bali, and suggests that a significant number of individuals with schizophrenia who need medical treatment are present in the community.

The subjects in the Never-treated group showed significantly higher total PANSS scores than did those in the Treated group. The present study demonstrated that one reason why subjects did not undergo treatment was not their good clinical condition, but rather that the never-treated status might be causally related to their poor clinical condition. Therapeutic interventions for these subjects are essential. The association between a never-treated status among persons with schizophrenia and their poor clinical condition was also reported in rural China (Ran et al., 2001) and in India (Padmavathi et al., 1998), which are, to our knowledge, the only studies that have investigated never-treated individuals with schizophrenia in the community.

The present study demonstrated that schizophrenic patients without violent acts had no opportunity to receive medical treatment in this developing country setting. The motivation for seeking help from psychiatric treatment in schizophrenic patients arose only after violent behavior was observed. In contrast to this situation in Bali, in developed countries, many non-violent schizophrenic patients with less severe symptoms early in their course of illness may undergo medical treatment. This difference could explain the three-times higher percentage of assaults in schizophrenic patients with their first-in-lifetime contact with a helping agency observed in developing than in developed countries, a finding from the study done by Volavka et al. (1997) based on reanalysis of the data of Determinants of Outcomes of Severe Mental Disorders (DOSMD) coordinated by the WHO (Jablensky et al., 1992). One of the key factors of an intervention strategy aimed at reducing never-treatment of schizophrenia in Bali is to provide motivation for treatment among patients without violent behavior, their families, and the community to which they belong. On the other hand, all subjects in this study sought treatment from a traditional healer in the community regardless of the presence or absence of violent behavior. We hypothesize that individuals with schizophrenia whose violent behavior disappeared during their treatment by a traditional healer were allowed to stay in the community while receiving care, whereas those with persistent violent behavior were taken to a mental hospital as a last resort. Although our data cannot confirm this hypothesis directly, this could explain why some patients who had a history of violent acts remain untreated in the present study. If mental health services are easily accessible and available in the community, in the same way as traditional healing, most schizophrenic patients might undergo prompt medical treatment. Resources and services for mental disorders are insufficient when considering the burden caused by these dis-

orders in both developing and developed countries (World Health Organization, 2001). The WHO report showed that the median number of psychiatrists for all countries is one per 100,000 people, and the median number of total psychiatric beds for the world population is 1.6 per 10,000 people. In Bali, the respective numbers are 0.46 and 0.85; thus, the resources and services for managing mental patients are poor relative to even the low world average.

In addition to the negative aspects of mental health in developing countries, we should also note several positive aspects. In Bali, a significantly lower prevalence of high expressed emotion among key relatives of individuals with schizophrenia was observed relative to Tokyo, an industrialized society also located in Asia (Kurihara et al., 2000b). Moreover, general residents in Bali expressed a more favorable global attitude towards persons with a history of psychiatric treatment than did those in Tokyo (Kurihara et al., 2000a). In this study, the subjects in the never-treated group were as well adapted socially as the subjects in the treated group despite having higher symptom levels. It suggests a high level of tolerance either by families or community members for symptoms other than violent behavior, and suggests that this tolerance enables affected individuals to live more easily in the community than would be expected in a developed society. To mobilize such important human resources for the psychiatric treatment of individuals with schizophrenia in Bali, making knowledge of the mental health services available to them is essential.

This study has several limitations. First, the targeted general population was somewhat small to investigate a prevalence of schizophrenia. Second, not a cross-sectional but a longitudinal follow-up is needed to assess the subject's clinical symptoms. Third, more comprehensive investigation into the various factors associated with the never-treated status of schizophrenia is desirable. Future study must overcome these limitations, and it should identify a mental health service model that can be used to treat as many individuals with schizophrenia as possible in Bali.

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Eleven-year clinical outcome of schizophrenia in Bali

Kurihara T, Kato M, Reverger R, Tirta IGR. Eleven-year clinical outcome of schizophrenia in Bali.
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Objective: To contrast the short-term and long-term outcome of schizophrenia in Bali.
Method: The clinical outcomes of 46 schizophrenic patients (DSM-IV-TR) consecutively admitted to Bangli Mental Hospital were evaluated by Positive and Negative Syndrome Scale (PANSS) and Eguma's Social Adjustment Scale (ESAS) at a 11-year follow-up, which was subsequent to a 5-year follow-up.
Results: Neither the PANSS score nor the ESAS score were significantly different, and there was a significant correlation between the two follow-up data. Subjects categorized into either the best or worst outcome group at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up more often than those who were categorized into the medium outcome groups at the 5-year follow-up.
Conclusion: The 5-year outcome of schizophrenia strongly predicted the 11-year outcome, especially for subjects who had gone into either a remissive or severe deterioration state within 5 years.

T. Kurihara[1], M. Kato[2], R. Reverger[3], I. G. R. Tirta[4]

[1]Komagino Hospital, Tokyo, [2]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan, [3]Wangaya General Hospital, Bali and [4]Bangli Mental Hospital, Bali, Indonesia

Key words: schizophrenia; follow-up studies; outcome assessment; developing countries

Toshiyuki Kurihara, Komagino Hospital, 273 Uratakao, Hachioji, Tokyo 193-8505, Japan.
E-mail: kurihara@sj8.so-net.ne.jp

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Significant outcomes

- The result indicating that 43.5% of patients had achieved either remission or partial remission at 11-year follow-up raised questions about the established, pessimistic view towards the chronicity of schizophrenia.
- Medium-term (5 year) outcome of schizophrenia strongly predicted long-term (11-year) outcome in Bali where only a minority of patients receive maintenance treatment.
- If an intervention strategy combining relevant maintenance medication with social support is conducted successfully in the future, the overall outcome of schizophrenia in Bali may improve over the longer term.

Limitations

- The relatively small sample size.
- The hospital-based sample may be a major source of bias.
- The investigation of predictors of outcome may be hindered by the limited number of outcome variables or by the lack of some important clinical data at inclusion.

Introduction

Outcome studies of schizophrenia are important given that diagnostic concepts are based in part on assumptions about outcome, and baseline data in this area are essential for psychiatrists for their clinical practice (1). Moreover, such studies could be useful for the evaluation of treatment effects with different modes of treatment, and they have the potential to improve clinical subtyping of patients

with schizophrenia. Dementia praecox was initially regarded as an illness leading to an inevitable non-remitting endstate over time; however, subsequent outcome studies have revealed a different and more optimistic pattern of courses for schizophrenia. Davidson and McGlashan (2) reviewed follow-up studies of schizophrenia, and found that although a broad heterogeneity exists in long-term outcome, 21–57% of subjects achieve a good outcome, ranging from mild impairment to recovery. Furthermore, it was demonstrated that the medium- to long-term course of schizophrenic patients shows a high degree of stability, suggesting that the illness tends to reach a plateau of psychopathology early in the course (1, 3–6). Jeste et al. (7) also stated that the course of schizophrenia in late life appears stable. However, it remains unclear whether this outcome stability is also observed in developing countries where only a minority of patients undergoes regular maintenance treatment.

Longitudinal follow-up studies from Asian countries reported a good outcome of schizophrenia in Hong Kong (8), Singapore (6, 9), and India (10). The predictor of a good outcome was a shorter length of illness before admission in both studies in Singapore. The International Pilot Study on Schizophrenia (11, 12) and the subsequent Determinants of Outcomes of Severe Mental Disorder (13) by the World Health Organization indicated that the course and outcome of schizophrenia was more favorable in developing than in developed countries. However, as Singapore and Hong Kong should not be categorized as developing but rather developed countries, Lee et al. (8) concluded that the concept of developing or a developed country as a predictor of the long-term outcome of schizophrenia is not applicable, at least to the two sites in Asia. They also stated that traditional Asian family-based cultures may contribute to the good outcome of schizophrenia. In contrast, Ran et al. (14) demonstrated that the clinical outcome of schizophrenia in a rural Chinese community was poor, especially for patients who had never received antipsychotic drug treatment because of either financial problems or a lack of relative's knowledge of schizophrenia. Even today, there is a dearth of long-term outcome studies on schizophrenia in Asia (9); thus, more research findings are needed from other Asian countries to allow for discussion on the outcome of schizophrenia in this area.

Aims of the study

The aim of the study is to investigate the long-term (11-year) outcome of schizophrenia in Bali, and to contrast the outcome with that of short-term follow-up (5-year). We hypothesized that the 11-year outcome would be worse than the 5-year outcome, because only a minority of patients receive maintenance treatment in this developing country setting.

Material and methods

Study area

Bali is located in South-east Asia and is one of more than 10 000 islands that make up Indonesia. It is famous as a tourist resort and for its unique Hindu-based culture. There are 3 048 317 people living in Bali (2001; at the 11-year follow-up) and the island is almost entirely ethnically and culturally homogeneous. The industry is now in the developing stages. The basic unit of society is a community referred to as 'banjar', which consists of several hundred households. Both the religious ceremonial aspect and social activity of the 'banjar' is recognized as essential in Bali. Bali had 260 psychiatric beds at the 11-year follow-up, of which 225 were at the Bangli Mental Hospital, the primary mental health facility on the island, with a further 25 at a private mental hospital and 10 at a general hospital. The number of psychiatric beds on the island at the 11-year follow-up was almost the same as that at the 5-year follow-up when there were 270 psychiatric beds with 225 at Bangli Mental Hospital, 25 at a private hospital, and 20 at a general hospital. The only difference between the two points was that there were 10 fewer beds at the general hospital.

Subjects and criteria

Details were described in our previous 5-year follow-up study (15). In brief, the subjects were 59 consecutive patients who had been hospitalized at the Bangli Mental Hospital in Bali (Indonesia) with no prior psychiatric treatment between January 1990 and April 1991 and whose diagnosis met PPDGJ-II Criteria (16) for schizophrenia. The subjects represent nearly all schizophrenic patients who were seeking psychiatric admission at that time, given that the hospital accounts for approximately 87% of the psychiatric beds in Bali. The screening criteria of PPDGJ-II for schizophrenia are identical to those of DSM-III (17). No subjects had comorbidity of either organic mental disorders or psychoactive substance-abuse disorders. At the previous 5-year follow-up, of the 59 subjects, 51 (86.4%) could be followed up. In the present

study, at the 11-year follow-up, 46 (78.0%) could be followed up. All 46 subjects were re-diagnosed as having schizophrenia according to DSM-IV-TR criteria (18). Five dropped out because of death due to a physical disease.

Follow-up interview

The clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (19, 20). The validity and reliability of the Indonesian version has been established (21). We used Eguma's Social Adjustment Scale (ESAS) (22, 23 and see Appendix) for the assessment of social adjustment. After those assessments, the rater asked the subjects about their medication status. All of the subject's evaluations were based not only on their clinical interview but also on information from family members. The rater was blind to the clinical assessment at the 5-year follow-up. Inter-rater reliability between the rater in the present study and the rater at the 5-year follow-up was established, giving a reliability of 0.83 with the PANSS according to analysis of variance (ANOVA) interclass correlation coefficient (ICC) (24) and a reliability of 0.82 with the ESAS according to the ICC (25). In addition to these main outcome indexes, we also investigated the readmission rate, duration of readmission, work status, and marital status to demonstrate the overall outcome of the subjects. Information regarding medication status and readmission sometimes did not coincide completely among informants, and thus information was derived not only from interviews but was also corroborated by medical records. One characteristic of the study is that the medication status of the subjects between the two points is clearly shown, and most subjects had been either non-medicated or on irregular medication due to the developing country setting. The study was approved by the Indonesian Institute of Science, and all subjects gave written informed consent to participate in the study.

Statistical analysis

To compare the overall clinical outcome between the 5-year follow-up and 11-year follow-up, we developed a point scoring system from 1 to 5 to quantify the range from (A) Self-supportive to (E) Hospitalized on the ESAS. Two-tailed *t*-test and Pearson's correlation were used for the comparison of the PANSS score and the ESAS score between the two points of follow-up. For a detailed comparison, we divided subjects into good (subjects with a score in the bottom 33rd percentile/cutoff score 53), moderate (subjects with a score in the 33rd to 67th percentile/cutoff score 95), and poor (subjects with a score in the top 33rd percentile/score with 96 or over) outcome categories according to the PANSS assessment at the 5-year follow-up. When we divided subjects into the three groups at the 11-year follow-up, the above-mentioned cutoff score was used. Chi-squared test was used for the comparison of the PANSS groups and the ESAS categories between the two follow-up points.

A multiple regression analysis was conducted to investigate the predictors of outcome. Either the PANSS scores or the ESAS scores at the 11-year follow-up were used as the dependent variable, with age at onset, age at inclusion, sex, educational period, number of family members, and duration of untreated psychosis (DUP) as independent variables.

Moreover, Kruskal–Wallis test was employed to investigate the difference between either the PANSS scores or the ESAS scores at the 11-year follow-up among subjects with regular medication, irregular/brief medication, and non-medication.

Results

Sample description

Of the 46 subjects, 27 were males and 19 were females. Subjects had a mean age of 26.7 years (SD 7.83) at the first entry, mean educational period of 6.3 years (SD 3.48), mean age at onset of 24.3 years (SD 6.94), mean length of first hospitalization of 35.0 days (SD 28.8), DUP of 27.9 months (SD52.50), and mean number of family members of 5.0 (SD 2.30). No subjects lived alone.

Overall outcome at 11-year follow-up

The mean positive, negative, general psychopathology, and total scores on the PANSS of 46 subjects at the 11-year follow-up were 17.91 (SD 9.87), 20.11 (SD 11.31), 36.48 (SD 13.93), and 74.50 (SD 33.61), respectively. Of 46 subjects, 11 (23.9%) were in remission and nine (19.6%) were in partial remission defined by DSM-IV-TR. Eighteen subjects (39.1%) were classified on the ESAS as 'self-supportive', six (13.0%) as 'semi-self-supportive', seven (15.2%) as 'socially adjusted to family or community', 15 (32.6%) as 'maladjusted', while none were classified as 'hospitalized'. Seven-

teen subjects (37.0%) worked full-time, 10 subjects worked part-time (21.7%), and 19 subjects (41.3%) did not work at all. Of 46 subjects, 28 (60.9%) had been re-hospitalized after inclusion in the study, and the mean length of readmission was 63.8 days (SD 104.8). No subjects were hospitalized at follow-up. Twenty-nine (63.0%) had been married, and of those, one was divorced and one was widowed.

Relationship between sociodemographic data and outcome

Age at onset, age at inclusion, sex, educational period, number of family members, and DUP did not predict the clinical outcome at the 11-year follow-up as measured by the PANSS or the ESAS.

Relationship between medication status and outcome

Between the 5- and 11-year follow-ups, seven (15.2%) had been on regular medication, 16 (34.8%) had been on medication at irregular intervals or at some point during the period, while 23 (50.0%) had never undergone medical treatment during the period. Eight subjects (17.4%) were on medication at the 11-year follow-up interview. Both the subjects in the regular medication group and those in the irregular/brief medication group tended to have higher scores both on the PANSS and ESAS than did subjects in the no-medication group; however, this difference did not reach the level of statistical significance (Table 1).

Relationship between 5-year and 11-year clinical outcome

The PANSS score was not significantly different between the 5- and 11-year follow-up [74.37 (SD 32.17) vs. 74.50 (SD 33.61)], and it was significantly correlated between the two points of follow-up ($r = 0.870$; $P < 0.0001$). Moreover, the ESAS score was not significantly different between the 5- and 11-year follow-up [2.26 (SD 1.10) vs. 2.44 (SD 1.33)], and it was significantly correlated between the two points of follow-up ($r = 0.755$; $P < 0.0001$). As to the PANSS for three groups, both those in the good outcome group and those in the poor outcome group at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up more commonly than did those who were categorized into moderate outcome groups ($P < 0.05$) (Table 2). As for ESAS, both those in the best category 'self-supportive' and those in the worst category 'maladjusted' at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up than did those who were categorized into either 'semi-self-supportive' or 'socially adjusted to family or community' ($P < 0.001$) (Table 3).

Discussion

Stability of long-term outcome of schizophrenia

In the present study, the 5-year outcome of schizophrenia strongly predicted the 11-year outcome. Thus, the result failed to support our original hypothesis that the 11-year outcome would be worse than the 5-year outcome in Bali where only a minority of the patients receives maintenance treatment. The percentages of subjects who were on regular medication during the two follow-up points and that of those who were on medication at the time of 11-year follow-up were only 15% and 17%, respectively. Nevertheless, the present results replicated other outcome studies carried out in developed countries demonstrating that the medium- to long-term course of schizophrenic patients was stable and revealed neither marked deterioration nor significant improvement, suggesting that the illness tends to reach a plateau of psychopathology early in the course (1, 3–6). Of these studies, the percentage of subjects on medication at follow-up was 59% (1) and 76% (4), respectively, and the percentage of subjects who underwent treatment at follow-up was 60% (5) and 52% (6), respectively. Why is the long-term outcome of schizophrenia stable not only in the developed countries but also in this non-industrialized society where only a minority of the patients received regular maintenance medication? We hypothesize that there may be therapeutic

Table 1. Medication status and clinical outcome at 11-year follow-up

	PANSS score (SD)	ESAS score (SD)	Symptom status		
			Remission (%)	Partial remission (%)	Symptomatic (%)
Regular medication group ($n = 7$)	79.00 (30.87)	2.57 (1.27)	1 (14.3)	2 (28.6)	4 (57.1)
Irregular/brief medication group ($n = 16$)	85.63 (33.08)	2.88 (1.20)	1 (6.3)	4 (25.0)	11 (68.8)
No medication group ($n = 23$)	65.39 (33.49)	2.09 (1.38)	9 (39.1)	3 (13.0)	11 (47.8)

Kruskal–Wallis test was used for comparison of either the PANSS score or the ESAS score among the three groups. No significant differences were found.

Table 2. PANSS groups at two points of follow-up

	11-year follow-up			Category change	
	Good (%)	Moderate (%)	Poor (%)	Same (%)	Changed (%)
5-year follow-up					
Good	15 (88.2)	2 (11.8)	0 (0)	15 (88.2)	2 (11.8)
Moderate	3 (18.8)	8 (50.0)	5 (31.3)	8 (50.0)	8 (50.0)
Poor	1 (7.7)	1 (7.7)	11(84.6)	11 (84.6)	2 (15.4)

Chi-squared test was used for the category change among the three groups between the two points. Significant difference was found ($P < 0.05$).

factors associated with stable long-term outcome of schizophrenia besides maintenance psychiatric medication. In Bali, sociocultural factors such as a supportive and favorable emotional environment for schizophrenic patients [both among family members (26) and the general public (27)], a working environment that facilitates the schizophrenic patients to work at jobs suited to their decreased ability, and traditional healing frequently used by the patients might be therapeutic. Although we could not prove this hypothesis directly from our data in this study, it is plausible that these community-based support systems prevent further deterioration of the course of the illness.

Prospect of the outcome of schizophrenia in longer term

Detailed analysis in the present study showed that subjects categorized either into best or worst outcome groups at the 5-year follow-up tended to be classified into the same category at the 11-year follow-up than those who were categorized into medium outcome groups at the 5-year follow-up. The result suggests that the progression, either amelioration or deterioration, in psychopathology and social functioning of schizophrenic patients stabilizes within 5 years, especially for those who either recovered to a remissive state or progressed to a severe deterioration state. Patients with relatively moderate symptoms tend to fluctuate in their outcome still at the 11-year follow-up. Ogawa et al. (23) followed up 140 schizophrenic patients over a period of 21–27 years and found that fluctuating courses of social functioning in the early stage of the illness showed differentiation on the whole to two directions in the later stage, namely to either a 'stable self-supportive' state or a 'chronic institutionalized' state. Whether the subjects in the present study in this developing country setting will reveal such a bipolarization over a longer term needs to be investigated in the future.

Transcultural comparison with other Asian countries

Factors that make it difficult to compare the present study findings with those of other outcome studies may include differences in the diagnostic criteria, duration of follow-up, sample size, and the terms of 'good' outcome. However, it is worthwhile to try to make such a transcultural comparison with neighboring countries in Asia. Kua et al. (6) followed up schizophrenic patients for 20 years in Singapore, and revealed that the percentage of patients categorized into either good or fair outcome based on aggregation of work and treatment status was 65%. Lee et al (8) followed up first-onset schizophrenic patients for 15 years in Hong Kong, and found that 53% of the subjects were recovered according to Bleuler's Severity Scale, while 21% of the subjects were rated as having a good psychosocial adjustment according to the Global Assessment of Functioning Disability ratings. Moreover, Thara (10) demonstrated that 59% of the schizophrenic patients were asymptomatic at the syndromal level on the Present State Examination (9th edn) at 20-year follow up in their Madras Longitudinal Study in India. All three of the above studies concluded that the outcome of schizophrenia was better than that in Western developed countries. In the present study, if we define good outcome as either remission or partial remission defined by DSM-IV-TR, 43.5% of the subjects in the present study fell into

Table 3. ESAS categories at two points of follow-up

	11-year follow-up				Category change	
	(A) Self-supportive (%)	(B) Semi-self-supportive (%)	(C) Socially adjusted to family or community (%)	(D) Maladjusted (%)	Same (%)	Changed (%)
5-year follow-up						
(A) Self-supportive	13 (81.3)	2 (12.5)	1 (6.3)	0 (0)	13 (81.3)	3 (18.8)
(B) Semi-self-supportive	3 (33.3)	2 (22.2)	3 (33.3)	1 (11.1)	2 (22.2)	7 (77.8)
(C) Socially adjusted to family or community	2 (14.3)	2 (14.3)	3 (21.4)	7 (50.0)	3 (21.4)	11 (78.6)
(D) Maladjusted	0 (0)	0 (0)	0 (0)	7 (100)	7 (100)	0 (0)

Chi-squared test was used for the category change among the four groups between the two points. Significant difference was found ($P < 0.001$).

the category. Moreover, in terms of social adjustment, 39.1% of the subjects were classified as 'self-supportive' on the ESAS. Thus, the outcome of schizophrenia in Bali was slightly worse than that of other Asian countries, given that the rate of good outcome observed was lower.

The percentage of hospitalized subjects at follow-up was 6.9% in Singapore (6), 9% in Hong Kong (8), and 3.3% in India (10), whereas no subjects were hospitalized at follow-up in this study. These small numbers of hospitalized patients in these Asian countries may reflect the high levels of family involvement in patient's care, which prevent long-term confinement in institutions (28). All subjects in this study lived with their family, and the percentage of single subjects was 41%, which was lower than that in Singapore (80%) (6) and in India (60%) (10).

Predictor of the outcome

No sociodemographic predictors of outcome were found in this study. Clinical factors, including modality of treatment, mode of delivery, and comorbidity of either organic mental disorders or psychoactive substance abuse disorders, did not differ among the subjects. The supportive and favorable attitude toward schizophrenic patients observed among the family members (26) and general residents (27) in Bali may have contributed to overall outcome. However, it is impossible to determine from the present data whether these factors are a predictor of outcome, because all subjects seemed to be blessed with the good emotional environment uniformly.

Maintenance medication and outcome

The clinical outcome revealed by the PANSS and ESAS of non-treated subjects tended to be better than that of medicated subjects, although the tendency was not statistically significant. As the efficacy of antipsychotics is well established (14, 29), it is not plausible that the lack of maintenance medication positively affected the long-term outcome of schizophrenia. The results reflect the finding that most patients in remission withdrew from maintenance treatment in this developing country setting.

However, it should also be noted that roughly half of non-medicated subjects were symptomatic. Furthermore, 69% of the subjects in the irregular/brief medication group were also symptomatic. The inadequate level of treatment offered to these patients might relate to the finding that the overall outcome of schizophrenia in Bali is somewhat worse than that of other Asian countries. An appropriate therapeutic intervention for these patients is essential. If an intervention strategy combining relevant maintenance medication with social support is conducted successfully in the future, the overall outcome of schizophrenia in Bali may improve over the longer term.

Limitations

The present study has several limitations. First, the small number of subjects made it rather difficult to interpret the results. Secondly, the outcome variables were limited. Thirdly, our hospital-based sampling method may have missed a significant number of schizophrenic patients who remained untreated in the community. Finally, clinical data at inclusion (e.g. mode of onset, premorbid function, either PANSS or ESAS assessment), which can be used as predictors of outcome, was lacking.

In conclusion, the 5-year outcome of schizophrenia in Bali strongly predicted the 11-year outcome, especially for subjects who had gone into either a remissive or severe deterioration state within 5 years. Previous studies performed in developed countries demonstrated that the medium- and long-term course of schizophrenic patients shows a high degree of stability, suggesting that the illness tends to reach a plateau of psychopathology early in the course. The present study replicated these finding in a developing country where only a minority of subjects underwent maintenance treatment.

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Appendix: Eguma's Social Adjustment Scale

(A) Self-supportive:

i) Has returned to a level of social functioning similar to that prior to onset of illness;
ii) Maintains an independent social life with or without asking any advice from psychiatrists or acquaintances;
iii) Maintains a normal family life (housewife, for example).

(B) Semi-self-supportive:

i) Displays vocational ability, with some occasional failures;
ii) Maintains a positive attitude towards work, but needs supervision and guidance;
iii) Maintains a normal life at home, but hesitates to return to the job held prior to onset of illness.

(C) Socially adjusted to family or community:

i) Works when encouraged with continuous significant support from others;
ii) Needs more time before being ready to return to previously held job;
iii) Able to work continuously if the work is kept at a simple level.

(D) Maladjusted: social adjustment not possible:

i) Non-productive life (able to be cared for at home);
ii) Anti-social (admission to psychiatric hospital necessary).

(E) Hospitalized: in psychiatric hospital.

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Separate Processing of Different Global-Motion Structures in Visual Cortex Is Revealed by fMRI

Shinichi Koyama,[1,2] Yuka Sasaki,[2] George John Andersen,[3] Roger B.H. Tootell,[2] Masato Matsuura,[4] and Takeo Watanabe[1,*]
[1] Department of Psychology
Boston University
64 Cummington Street
Boston, Massachusetts 02215
[2] NMR Center
Massachusetts General Hospital
Charlestown, Massachusetts 02129
[3] Department of Psychology
University of California, Riverside
Riverside, California 92521
[4] Tokyo Medical and Dental University
1-5-45 Yushima, Bunkyo-ku
Tokyo 113-8510
Japan

Summary

The visual system has the remarkable ability to extract several types of meaningful global-motion signals, such as radial motion, translation motion, and rotation, for different visual functions and actions. In the monkey brain, different groups of cells in MST respond best to different types of global motion [1, 2], whereas in lower cortical areas including MT, no such differential responses have been found. Here, we show that an area (or areas) lower than MST in the human brain [3] responds to different types of global motion. A series of human functional magnetic resonance imaging (fMRI) experiments, in which attention was controlled for, indicated that the center of radial motion activates the corresponding location in the V3A representation, whereas translation motion activates mainly in a more peripheral representation of V3A. These results suggest that in the human brain, V3A is an area that differentially responds according to the type of global motion.

Results and Discussion

Monkey single-unit recording studies have revealed that global-motion patterns such as rotation, radial motion, and translation motion [4–7] are processed distinctly in MST [1, 2, 8]. What evidence exists for motion processing in human brains? In contrast to monkey brains, the results of several studies suggest that V3A in human brains is highly motion selective [9, 10]. V3A is regarded as an earlier stage of visual processing than MST [3]. Greater activation with coherent motion (velocities in a single general direction), as compared with random motion, was found in V3A but not in V1 [11–13]. However, how human V3A responds to different types of global motion has not been addressed. In the present paper, we show that human V3A differentially responds according to the type of global motion.

To measure global-motion activity in multiple areas, we presented human subjects with displays of radial motion, translation motion, and random motion. Radial motion is an important source of information for locomotion (e.g., heading) and can be either expansion or contraction. Translation motion is a pattern whose direction is perceived as the average of signals of randomly moving dots within a certain range of directions [14–17]. In the present study, we found that in human V3A, greater activity was associated with retinotopic locations corresponding to the focus of expansion (FOE) as compared to activity to random motion, whereas regions associated with more peripheral retinotopic regions were more activated with translation motion than random motion.

To assess activation based on global-motion type, we used a standard method of comparing MR activity to a specific global-motion type with activity to random motion. The stimuli consisted of limited-lifetime dots to ensure that the activity of units sensitive to local motion was statistically the same for global-motion stimuli and random-dot stimuli. Thus, if a difference in activity is found between a global type of motion and a random-motion pattern in some area, it would be regarded as a result of response to a pattern on a global scale [11, 12, 18, 19] rather than local motion.

In order to compare activity of different motion types, we systematically controlled for two confounding factors: opponent-motion suppression and attention. Opponent-motion suppression refers to activity of cells for neighboring opponent-motion direction signals [20, 21]. Opponent-motion suppression has been found in monkey MT [20] or human MT+ [21], but not in V1 for either species. This finding could make the brain respond differently to translation motion and random motion. For example, a translation motion in which dots move within ±45° from the spatiotemporal average has no dots moving in opposite directions, whereas in a random-motion display, two dots could move in opposite directions within a neighboring region. Thus, higher MT+ activity in the presence of translation motion as compared with random motion can be attributed to the lack of opponent motion in the global flow. To control for this factor, we used a *transparent*-translation-motion display in which half of the dots moved randomly within a 45° range and the other half within the opposite 45° range (e.g., 0° to 45° and 180° to 225°). As a result, two transparent-translation motions in opposite directions were perceived (Figures 1A and 1B). For this manipulation, the probability of local dots moving in opponent directions (within a local region) for the translation-motion display was statistically higher than in the random-motion display. The presence of a high degree of opponent motion, as compared to little or no opponent motion, results in lower MR activity. Thus, higher activity for transparent-translation motion as compared to random motion would be the result of the global flow pattern and not opponent suppression.

*Correspondence: takeo@bu.edu

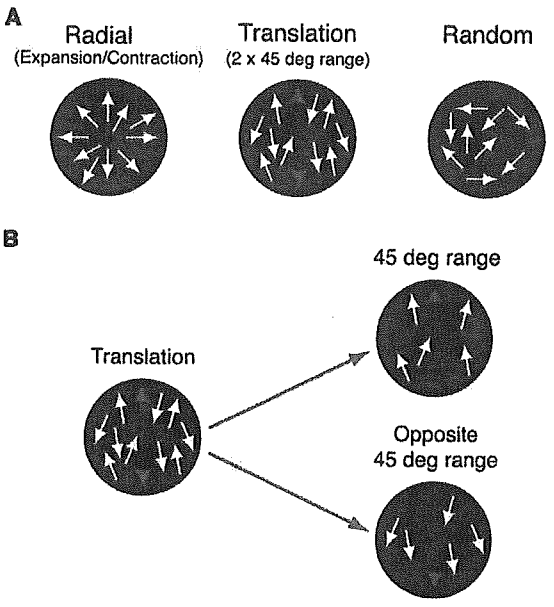

Figure 1. A Schematic Description of the Motion Stimuli

(A) The subjects viewed a radial-motion, translation-motion, or random-motion stimulus in 16 s epochs. The global-motion types were changed in a random order every 16 s.

(B) The translation-motion display consisted of two sets of global motion. In one set, the motion directions of the dots were limited to a 45° range, whereas in the other set, the motion directions of the dots were limited to the opposite 45° range. The two sets of global motion were perceived as transparent motion.

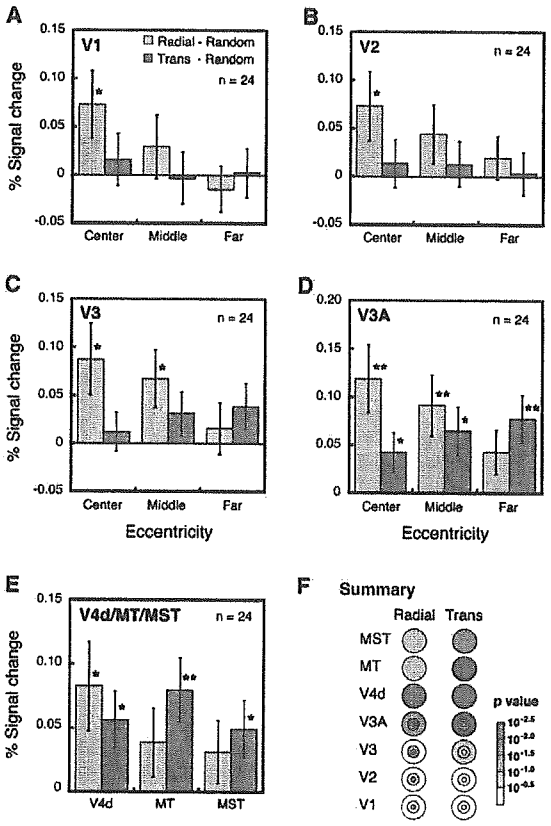

Figure 2. Mean MR Signal Amplitudes for Each Visual Area for Each Eccentricity

Each column represents the average of 24 data, i.e., 6 subjects × 4 time points. Error bars indicate the standard errors. The * sign indicates significant difference between radial motion (or translation motion) versus random motion ($p < 0.05$). The ** sign indicates $p < 0.01$. The red color scale in the summary (F) indicates p values from the paired t test for radial motion versus random motion (left column) and translation motion versus random motion (right column) for each visual area (V1, V2, V3, V3A, V4d, MT, and MST). Three concentric circles in V1, V2, V3, and V3A represent eccentricity (center < 2°, middle < 5°, and far > 5°) in those visual areas. Radial motion produced significantly stronger MR signals than random motion in the following visual areas: central V1 ($p < 0.05$), central V2 ($p = 0.052$), central and middle V3 ($p < 0.05$), central and middle V3A ($p < 0.05$), and V4d ($p < 0.05$). On the other hand, translation motion produced significantly stronger MR signals than random motion in central and middle V3A ($p < 0.05$), far V3A ($p < 0.01$), V4d ($p < 0.05$), MT ($p < 0.01$), and MST ($p < 0.05$).

As for attention, we asked subjects to perform a well-established task [22, 23] that was independent of the global-motion type. Each trial lasted for 4 s. During the first 1980 ms, a motion stimulus was presented. The subjects had to respond in the remaining 2020 ms. During the 1980 ms presentation, the speed of motion was different between the first and second intervals (both 990 ms) of a motion-stimulus presentation. Subjects were instructed to press a response key to indicate which of the two intervals had a greater speed. The same motion-speed discrimination task was given in all of the three motion types in order to ensure that subjects attended equally in all motion conditions [22, 23].

There were four trials in each epoch of 16 s. In each epoch, the same type of motion was presented: For transparent-translation motion, each of four pairs of direction ranges covering 90° in total was presented on each trial, so that 360° motion directions were covered in an epoch. For radial motion, in two trials, dots moved outward (expansion) from the center of the display, whereas in the other two trials, they moved inward (contraction). The presentation order of the four trials was randomized. For random motion, local dots moved within the 360° range for an entire epoch. The dot density was kept constant throughout the region in all the types of motion so that local-motion signals were equivalent. Within one scan, the same set of local-motion signals were presented for the three types of motion. We measured fMRI activity on a flattened occipital patch that indicated the retinotopical locations in V1, V2, V3 [24, 25], the locations of MT/MST [26], and other areas including V4d [27], V3B [28], and KO [29] as well as V3.

A larger amount of MR signal for the radial motion or translation motion, as compared to the random motion, can be regarded as activity related to the overall pattern of radial or translation motion. The activity patterns for these two types of motion were dramatically different in these low-level stages. Figures 2A–2E and Figure 3 indicate that the general tendency of activity for translation motion increased with increasing eccentricity in relatively higher stages such as V3 and V3A. On the other hand, activity for radial motion decreased with increasing eccentricity in V1, V2, V3, and V3A. A two-way ANOVA for motion type (radial versus random motion)

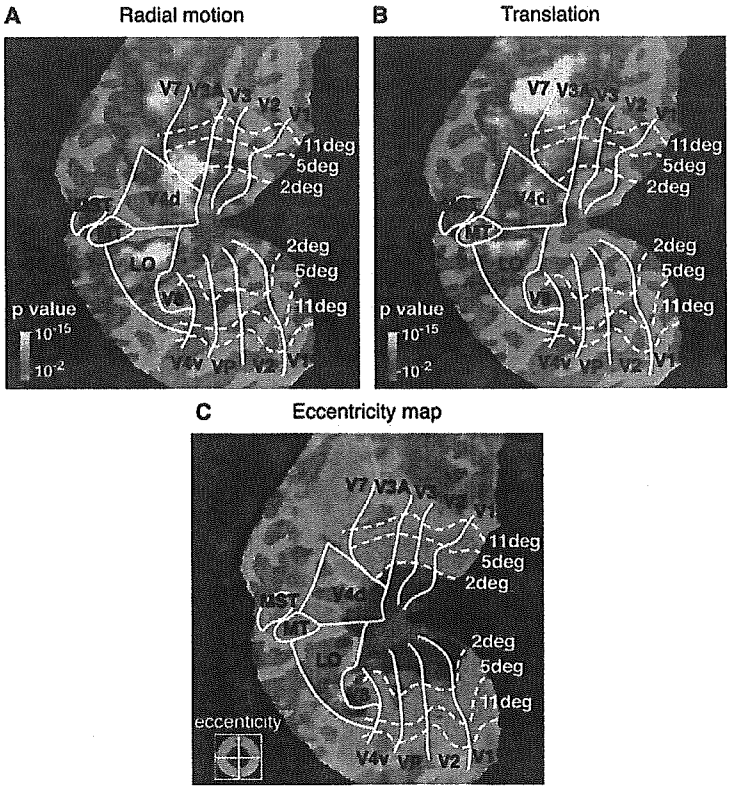

Figure 3. Activation Maps from the First Experiment

(A) Activation map for radial motion in a representative subject (left hemisphere). Average activation across six subjects was painted onto a flattened cortical map of a representative subject. For radial motion, activation was mostly seen in the central representation of V1 (<2°), V2 (<2°), V3 (<5°), and V3A (<5°).

(B) For translation motion, activation was seen in the peripheral V3 (>2°), V3A (>2°), and MT/MST.

(C) Eccentricity map of the representative subject obtained from a separate experiment. The red area in the image indicates voxels that responded maximally when the stimulus was presented in the fovea. The blue and green areas indicate voxels that responded maximally to the parafoveal and peripheral stimuli.

and eccentricity (center < 2°, middle < 5° versus periphery > 5°) was applied to V1, V2, V3, and V3A. A significant interaction between motion type and eccentricity was found in V1 ($p < 0.0001$), V2 ($p < 0.05$), V3 ($p < 0.01$), and V3A ($p < 0.0001$). The results of two-way ANOVA of motion type (translation versus random motion) and eccentricity showed that the interaction between motion type and eccentricity was significant in V3 ($p < 0.05$) and V3A ($p < 0.0001$).

These results were replicated in a control experiment (see Control 1 in the Experimental Procedures) in which the duration of the first and the second intervals varied randomly between 660 and 1320 ms (average duration was kept at 990 ms). This result excludes the possibility that the subjects paid attention to changes in motion speed, which could have been predicted to occur. In addition, because the probability of opponent local motion is higher with the transparent-translation-motion display than with the random-motion display, the higher activity with transparent-translation motion than with the random motion cannot be attributed to opponent suppression [20, 21].

In summary, the central representation of V1, V2, V3, and V3A was activated with radial motion, whereas the peripheral representation of V3A was activated with translation motion, suggesting that differential processing of global motion starts at least in V3A.

In the first experiment, FOE was presented at the center of the visual field. There are at least two possible explanations for the central representation in the low-level areas being more activated with radial motion. The central region of radial-motion stimuli has all directions of motion (all velocities point outward or inward in this region). In addition, the foveal representation in low-level visual areas has smaller receptive fields than more-peripheral representation. Thus, one possibility is that multiple populations of local directionally selective neurons may be excited particularly for the foveal representation because the central region of radial-motion stimuli contains all motion directions. The second possibility is that a specific pattern of radial motion around FOE drives a greater response.

To examine which possibility is plausible, we shifted the location of the FOE from the fixation point in a second experiment. If the activity is highest in the cortical location corresponding to FOE irrespective of whether FOE is presented in the central or peripheral visual field, then this finding would support the second possibility. In contrast, the first possibility does not predict this particular pattern of activity.

In the second experiment, we examined three conditions. In the first condition, FOE was presented at the fovea (the same location as in Experiment 1). In the second condition, FOE was shifted away by 4.5°. In the third condition, random motion was presented. The three conditions were alternated in a random order. The other aspects of the procedure were identical to the procedure used in Experiment 1.

As shown in Figure 4, when FOE was presented in the fovea, the pattern of results was very similar to the results for the radial-motion condition in Experiment 1. On the other hand, when FOE was presented in the 4.5° eccentricity (indicated as "the middle" in the figure), no particular signal enhancement was observed in V1,