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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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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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ARTICLE

The antipsychotic sultopride is overdosed – a PET study of drug-induced receptor occupancy in comparison with sulpiride

Akihiro Takano[1], Tetsuya Suhara[1], Fumihiko Yasuno[1], Kazutoshi Suzuki[1], Hidehiko Takahashi[2], Takuya Morimoto[1], Young-Joo Lee[3], Hiroyuki Kusuhara[3], Yuichi Sugiyama[3] and Yoshiro Okubo[4]

[1] *Brain Imaging Project, National Institute of Radiological Sciences, 9-1, Anagawa 4-Chome, Inage-ku, Chiba, Japan*
[2] *Asai Hospital, 38-1, Katoku, Togane, Chiba, Japan*
[3] *Department of Molecular Pharmacokinetics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan*
[4] *Department of Neuropsychiatry, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, Japan*

Abstract

Conventional antipsychotics tend to elicit extrapyramidal symptoms at clinical doses, but dose optimization could reduce the risk of such side-effects. In-vivo receptor-binding studies have suggested that 70–80% of dopamine D_2 receptor occupancy provides the desired antipsychotic effects without extrapyramidal symptoms. In terms of dose optimization based on the occupancy, there has not been enough supporting data regarding the clinical doses of the respective antipsychotics. In this study, we measured dopamine D_2 receptor occupancy of two conventional benzamide antipsychotics, sulpiride and sultopride, using positron emission tomography, to investigate the rationale of their clinical dose. Although they are prescribed at similar doses (300–1200 mg), the doses required to obtain similar receptor occupancy (70–80%) were quite different: 1010–1730 mg for sulpiride but 20–35 mg for sultopride. In terms of dose, sultopride has about 50 times greater potency than sulpiride based on dopamine D_2 receptor occupancy. Evidence for the optimal doses of conventional antipsychotics based on dopamine D_2 receptor occupancy would be helpful for rational antipsychotic therapy.

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Key words: Antipsychotics, dopamine D_2 receptor, dose settings, occupancy, PET.

Introduction

Conventional antipsychotics have been regarded as drugs with more frequent extrapyramidal side-effects (EPS) compared with second-generation antipsychotics (Gerlach and Peacock, 1995; Waddington et al., 1997). However, a recent meta-analysis suggested that low-potency conventional antipsychotics at optimal doses might in fact not induce more EPS than second-generation antipsychotics (Leucht et al., 2003), and another meta-analysis reported that second-generation antipsychotics were found not to have greater efficacy than high-potency conventional antipsychotics at lower dose (Geddes et al., 2000). Discussion on the scientific evidence for clinical doses of conventional antipsychotics has been inconclusive, and opposing results were also reported in a meta-analysis (Davis et al., 2003). Although antipsychotics are classified in several ways, in the present article, the term 'second-generation antipsychotics' refers to clozapine and all the novel antipsychotics introduced in the 1990s, and 'conventional antipsychotics' refer to older antipsychotics. The advent of positron emission tomography (PET) has made it possible to measure the receptor occupancy of antipsychotics in the living human brain (Farde et al., 1988). PET studies have suggested that a range of 70–80% of dopamine D_2 receptor occupancy provides the desired antipsychotic effects without EPS (Farde et al., 1992; Kapur et al., 2000). It was also suggested that one advantage of the use of second-generation

Address for correspondence: T. Suhara, M.D., Ph.D., Brain Imaging Project, National Institute of Radiological Sciences, 9-1, Anagawa 4-chome, Inage-ku, Chiba, 263-8555, Japan.
Tel.: +81-43-206-3194 *Fax*: +81-43-253-0396
E-mail: suhara@nirs.go.jp

antipsychotics might be better explained by the determination of appropriate clinical dose settings (Kapur and Mamo, 2003). Amisulpiride, a benzamide antipsychotic drug, was reported to show fewer EPS and has been regarded as a second-generation antipsychotic drug; its clinical doses were reported to show appropriate dopamine D_2 receptor occupancy (Martinot et al., 1996). On the other hand, sulpiride and sultopride, other benzamide antipsychotics, were considered as conventional antipsychotics. Despite their similar registered clinical doses (sulpiride 300–600 mg, max 1200 mg; sultopride 300–600 mg, max 1800 mg in Japan) and the fact that the equivalency of clinical potency was reported (2 mg haloperidol is equivalent to 200 mg sulpiride or 200 mg sultopride) (Inagaki et al., 1999), sultopride has been reported to induce more EPS than sulpiride (Peselow and Stanley, 1982). The relationship between the dose/plasma concentration and dopamine D_2 receptor occupancy by the two drugs has not been fully explored. Since they are relatively selective dopamine D_2 receptor antagonists (Peselow and Stanley, 1982), their dopamine D_2 receptor occupancy in the living human brain can be expected to provide us with the criteria to decide the appropriate doses. In this study we measured dopamine D_2 receptor occupancy of the two conventional substitute benzamide antipsychotics, sulpiride and sultopride, to investigate the rationale for their dose settings.

Materials and methods

Subjects

Twenty-one male healthy volunteers (26.6 ± 5.7 yr) were enrolled in this study. None had a history of psychiatric or neurological illness, chronic somatic illness or substance abuse. None was receiving any medication, and none had a close relative with a known psychiatric illness.

After description of the study, written informed consent was obtained from all subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

Radioligand

The precursors of [^{11}C]FLB 457 were kindly supplied by Astra Arcus (Sodertaje, Sweden). [^{11}C]FLB 457 was synthesized by *O*-methylation of the corresponding precursors with [^{11}C]methyliodide with high specific radioactivity, which was obtained by a reduction of [^{11}C]CO_2 with $LiAlH_4$ in an inert atmosphere with specially designed equipment (Halldin et al., 1995; Suzuki et al., 1999). The radiochemical purities were more than 95%.

PET procedure

Dynamic scans were performed for 90 min using ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA) immediately after a bolus injection of 220 ± 16 MBq of [^{11}C]FLB 457 with high specific radioactivities (141 ± 34 GBq/μmol).

MRIs were acquired on Gyroscan NT (Philips Medical System, Best, The Netherlands) (1.5 T) to obtain T1-weighted images of the brain.

Two PET scans were performed, one before antipsychotics administration, and the second at the possible peak time of plasma concentration of the drugs, 3 h after a single dose of sulpiride (200–800 mg; 3 subjects at 200 mg, 3 at 400 mg, 3 at 600 mg, 2 at 800 mg) and 2 h after a single dose of sultopride (10–200 mg; 3 subjects at 10 mg, 3 at 25 mg, 2 at 50 mg, 1 at 100 mg, 1 at 200 mg). Three subjects with sultopride (50, 100, and 200 mg respectively) did not complete the 90-min PET scans due to akathisia and EPS, with PET data of 60 min being used for the subject receiving 200 mg and 70 min for the two subjects receiving 50 mg and 100 mg sultopride respectively. Blood samples were taken just before each PET scan for concentration measurements of sulpiride or sultopride.

The subjects were examined for EPS, akathisia, and other adverse effects after the PET scans by two psychiatrists who were aware of the dosage of the antipsychotics.

Data analysis

All emission scans were reconstructed with a Hanning filter cut-off of 0.4. Regions of interest (ROIs) (prefrontal cortex, temporal cortex, thalamus, cerebellum) were drawn on PET/MRI images by a template-based method (Yasuno et al., 2002). The average values of right and left ROIs were used to increase the signal-to-noise ratio for the calculations. Quantification of PET data was performed using a three-parameter simplified reference tissue model to estimate binding potential (BP) (Lammertsma and Hume, 1996). The cerebellum was used as the reference tissue because of its negligible density of dopamine D_2 receptors for calculation (Suhara et al., 1999). This model allows the estimation of BP, which was defined as the ratio of receptor density (B_{max}) to dissociation constant (K_d). Dopamine D_2 receptor

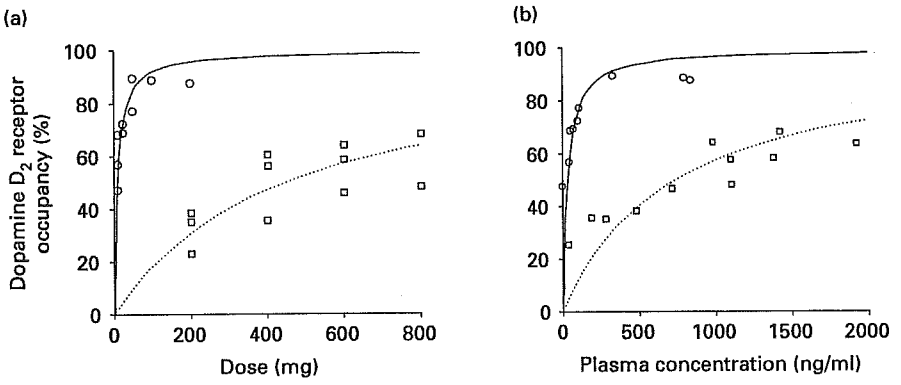

Figure 1. Relationship between dopamine D_2 receptor occupancy and doses of sulpiride and sultopride (a), and between dopamine D_2 receptor occupancy and plasma concentrations of sulpiride and sultopride (b). Mean dopamine D_2 receptor occupancy of three regions (prefrontal cortex, temporal cortex, and thalamus) was shown as dopamine D_2 receptor occupancy. Open squares indicate sulpiride, and open circles indicate sultopride. The dotted regression curve was fitted to the sulpiride data, and the solid regression curve was fitted to the sultopride data.

occupancy by antipsychotics was calculated using the following equation:

$$Occu = (BP_{baseline} - BP_{drug}) \times 100/BP_{baseline},$$

where Occu is receptor occupancy, $BP_{baseline}$ is BP in the drug-free state, and BP_{drug} is BP of the subject on the drug.

The relationship between dopamine D_2 receptor occupancy and dose/plasma concentration of antipsychotics was fitted to the following equation:

$$D_{2,occu} = 100 \times D/(ED_{50} + D),$$

where $D_{2,occu}$ is dopamine D_2 receptor occupancy, ED_{50} is the dose/concentration to induce 50% occupancy, and D is the dose/concentration of the drug (Fitzgerald et al., 2000; Kapur and Remington, 1996).

The measurement of plasma concentrations of sulpiride and sultopride

The plasma concentration of sulpiride was measured according to a previous report (Tokunaga et al., 1997) with the following modification. The HPLC column was a Waters Xterra RP18, a 150 × 3.9 mm i.d. with a mobile phase of 10% CH_3CN in 0.1 M phosphate buffer (pH 2.0) at a flow rate of 1.0 ml/min. A UV detector was set at 235 nm.

The plasma concentration of sultopride was measured according to a previous report (Kobari et al., 1985) with the following modification. The HPLC column was Waters Xterra RP18, a 150 × 3.9 mm i.d. with a mobile phase of 12% CH_3CN in 0.1 M phosphate buffer (pH 2.0) at a flow rate of 1.0 ml/min. A UV detector was set at 235 nm.

Results

The mean dopamine D_2 receptor occupancy in the three regions (prefrontal cortex, temporal cortex, and thalamus) ranged from 25.3% to 68.3% on doses of 200–800 mg sulpiride and from 47.4% to 89.4% on doses of 10–200 mg sultopride. Occupancy values of the three subjects taking sultopride and not completing the 90-min PET scans due to EPS or akathisia were more than 87%. No subjects taking sulpiride showed akathisia or EPS. None of the 21 subjects showed any other adverse effects. For both sulpiride and sultopride, mean dopamine D_2 receptor occupancy increased as the dose and plasma concentration increased (Figure 1a,b). There were no obvious differences in occupancy among the three regions. The S.D. of dopamine D_2 receptor occupancy among the three regions ranged from 0.9% to 10.2% (mean ± S.D., 5.1 ± 3.0%) for sulpiride and from 0.8% to 6.5% (4.3 ± 1.9%) for sultopride. The ED_{50} value of sulpiride was 433 mg ($r = 0.69$) for dose and 740 ng/ml ($r = 0.71$) for plasma concentration, while that of sultopride was 8.7 mg ($r = 0.85$) for dose and 32 ng/ml ($r = 0.66$) for plasma concentration.

Discussion

Despite the similar registered clinical doses for sulpiride and sultopride (Inagaki et al., 1999), the ED_{50} values measured by PET were quite different. Based

on the dopamine D_2 receptor occupancy, sultopride has approx. 20 times greater potency than sulpiride when viewing plasma concentration, and approx. 50 times greater potency in terms of dose. Calculating the optimal doses with this occupancy data, 1010–1730 mg sulpiride would be required to obtain 70–80% of dopamine D_2 receptor occupancy, while 20–35 mg sultopride would be sufficient. The calculated optimal dose range for sulpiride overlapped with the upper range of the registered clinical doses. On the other hand, the registered clinical doses of sultopride were approx. 10 times higher than the calculated optimal doses. Clinically, sultopride has been used for sedation rather than for the treatment of psychotic symptoms, and it was reported to have a high incidence of EPS (Peselow and Stanley, 1982). However, the present results suggest that a much lower dose of sultopride would be sufficient to treat psychotic symptoms. A future clinical trial would be required with such lower dose.

There are some pharmacological differences in the profiles of the two drugs. The affinity to dopamine D_2 receptor of sultopride (IC_{50} value 18 nM) was higher than that of sulpiride (69 nM) (Mizuchi et al., 1982). In addition, the brain uptake from blood was much higher for sultopride compared to sulpiride (Mizuchi et al., 1983). As the log *p* value was 1.46 for sultopride and 0.42 for sulpiride, the difference in brain uptake was considered to be due to the higher lipophilicity of sultopride (Mizuchi et al., 1983). Since drug transport is regulated by efflux transporters such as P-glycoprotein at the blood–brain barrier (Wang et al., 2004), we investigated the possibility of a *substrate* of P-glycoprotein for both drugs. However, we could not obtain supportive data for any *substrate* (data not shown). The different receptor occupancy profiles of the two drugs could be attributed to differences in drug affinity and penetration into the brain.

Despite the pharmacological differences, the clinical doses of the two drugs were determined as equivalent (Inagaki et al., 1999). Several potential problems concerning the process of determining the clinical doses of antipsychotics at the stages of both animal and clinical studies seem to exist. In a series of animal experiments, the inhibition of apomorphine- or methamphetamine-induced stereotyped behaviour and the induction of catalepsy were evaluated for sulpiride and sultopride (Araki et al., 1986). In the inhibition of apomorphine-induced stereotyped behaviour, sultopride was approx. 100 times weaker than haloperidol. For catalepsy induction, sultopride was approx. 25 times weaker than haloperidol (Araki et al., 1986). Although a series of paradigms such as the inhibition of apomorphine- and methamphetamine-induced stereotyped behaviours was used for animal studies, psychiatric symptoms in human patients could not themselves be modelled as in animals. The optimal dose in any such model will certainly not represent the dose for humans, making it difficult to estimate optimal doses for humans from animal experiments. Doses chosen on the basis of an animal study were often unrepresentative of the clinical condition (Kapur et al., 2003), and the doses in a clinical study tended to be higher than the minimum optimal dose (Talvik et al., 2004). In clinical studies, several preliminary reports were published in the 1970s regarding the use of sultopride in psychiatric disorders (Genevieve and Couriol, 1976; Maurel and Pujol, 1975; Robert, 1978). However, the doses in those reports were diverse, from 200 mg to 4800 mg, and a variety of patients were included (Peselow and Stanley, 1982). In a double-blind comparative study of sultopride (800–1600 mg) with thioproperazine (8–16 mg), EPS emerged for both drugs, and no differences in EPS were reported between them (Sizaret and Moreau, 1977). In a double-blind comparative study of sultopride with haloperidol, the dose (300–1800 mg/d) was defined on the basis of an animal study, a phase-two study and preliminary clinical data (Kudo et al., 1987). In that study, antiparkinsonian medications were allowed to be prescribed, and it was concluded that sultopride was as efficacious as haloperidol. However, the co-administration with antiparkinsonian medications might have masked any possible overdose. In another double-blind study for comparison between sulpiride (300–1800 mg) and sultopride (300–1800 mg), antiparkinsonian medications were also allowed (Kudo et al., 1986), and the effectiveness of the two drugs was judged to be not significantly different. Again, EPS might have been masked by the antiparkinsonian medications. In clinical studies for antipsychotics, symptoms and side-effects of patients with schizophrenia would not be easy to evaluate if also using antiparkinsonian medications.

Since the clinical doses of amisulpride were reported to show appropriate dopamine D_2 receptor occupancy (Martinot et al., 1996), one advantage of the use of second-generation antipsychotics might be better explained by the application of appropriate clinical dose settings.

Although sulpiride was introduced in the clinical field in the 1970s and is classified as a conventional antipsychotic (Ago et al., 2005; Keltner and Johnson, 2002), some reports considered it as an 'atypical' antipsychotic due to its low EPS rate (Caley and Weber, 1995; Rummel et al., 2003). The present result

indicated that the clinical doses of sulpiride overlapped with the lower range of the optimal doses. If the proper setting of the clinical dose explains the low rate of EPS, sulpiride could be regarded as 'atypical'.

There are several confounding factors in this study. First, we measured occupancy with normal subjects after a single administration. Although it is unlikely that there is a marked difference in dopamine D_2 receptor occupancy between normal subjects and patients with schizophrenia, further occupancy studies in patients with schizophrenia and repeated administrations may provide useful information. Second, although most previous occupancy reports were based on striatal measurements, we measured extrastriatal regions with [^{11}C]FLB 457 because limbic and cortical regions were suggested to be a site of antipsychotic actions (Lidow et al., 1998; Pilowsky et al., 1997). The test–retest reproducibility was good, with a mean variability of 4.5% for the thalamus, 7.7% for the frontal cortex, and 5.4% for the temporal cortex (Sudo et al., 2001). Although the regional differences of dopamine D_2 receptor occupancy by clozapine was reported (Pilowsky et al., 1997), there have been discussions on the methodology (Olsson and Farde, 2001) and similar occupancy values of antipsychotics were obtained in extrastriatal regions and the striatum in several studies (Nyberg et al., 1999, 2002; Takano et al., 2004; Talvik et al., 2001; Vernaleken et al., 2004; Yasuno et al., 2001). Thus, the threshold of dopamine D_2 receptor occupancy in the striatum was also considered to be applicable to extrastriatal regions. Third, 3 out of the 21 volunteers did not complete the 90-min PET scans, and their results were based on 60–70 min data. Nevertheless, the time to reach equilibrium was within 60 min in those regions, and a simplified reference tissue method has been reported to produce reliable BP for over 60 min (Olsson and Farde, 2001).

In summary, despite the similar registered clinical doses for sulpiride and sultopride, based on dopamine D_2 receptor occupancy, sultopride has ~50 times greater potency than sulpiride. As evidence for the clinical doses of conventional antipsychotics has been limited, their re-evaluation based on dopamine D_2 receptor occupancy is warranted for the establishment of rational antipsychotic therapy.

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Statement of Interest

None.

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Abnormal effective connectivity of dopamine D2 receptor binding in schizophrenia

Fumihiko Yasuno[a,b], Tetsuya Suhara[a,b,*], Yoshiro Okubo[c], Tetsuya Ichimiya[a,b], Akihiro Takano[a,b], Yasuhiko Sudo[a,b], Makoto Inoue[a,b]

[a]*Brain Imaging Project, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan*
[b]*CREST Japan Science and Technology Corporation, Saitama 332-0012, Japan*
[c]*Department of Psychiatry, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan*

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Abstract

Receptor binding has been examined region by region in both in vitro and in vivo studies, but less attention has been paid to the connectivity of regional receptor binding despite the fact that neurophysiological studies have indicated an extensive inter-regional connectivity. In this study, we investigated the connectivity of regional dopamine D2 receptor binding in positron emission tomography data from 10 drug-naïve patients with schizophrenia and 19 healthy controls. We applied a structural equation method to regional receptor binding. The results indicated that the network models of the patients and normal subjects were significantly different. As to the individual path coefficients, (a) connectivity between cortical regions was different between groups; (b) connectivity from the prefrontal cortex, parietal cortex, and thalamus to the anterior cingulate differed from that in controls; and (c) connectivity from the prefrontal cortex to the anterior cingulate and thalamus via the hippocampus was observed in normal subjects but not in patients. These results suggest that a systems-level change reflected in the connectivity of D2 receptor binding is present in schizophrenia.

Keywords: PET; Structural equation modeling; Dopamine; D2 receptor; Schizophrenia

1. Introduction

A number of morphological and neurochemical abnormalities have been found to characterize schizophrenia. In particular, the dopamine D2 receptor has been investigated extensively, since the chronic use of amphetamine can cause psychotic symptoms and dopamine D2 receptor antagonists are the most widely used drugs for the treatment of schizophrenia. We have recently reported a reduction of dopamine D2 receptor binding in the anterior cingulate of patients with schizophrenia (Suhara et al., 2002). On the other hand, abnormal inter-regional connectivity has been

* Corresponding author. Brain Imaging Project, National Institute of Radiological Sciences, 9-1, Anagawa 4-Chome, Inage-ku, Chiba 263-8555, Japan. Tel.: +81 43 206 3194; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

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reported in neurophysiological studies of schizophrenia. Interdependence between the different dopaminergic pathways arising in the ventral mesencephalon is a general property of this neuron group (Simon et al., 1988; Louilot et al., 1989). Dopamine systems interact with several other neurotransmitter systems with direct or indirect synaptic connections (Sulzer et al., 1998), and aberrant interactions among different neural networks could lead to an unusual inter-regional dopaminergic tone.

The present study used structural equation modeling to evaluate the connectivity of regional D2 receptor binding in schizophrenia patients and normal controls (McIntosh and Gonzalez-Lima, 1994; McIntosh et al., 1994; Horwitz et al., 1999) in earlier published data (Suhara et al., 2002) and new data from positron emission tomography (PET) and matching magnetic resonance imaging (MRI) (Fig. 1). By this method, the inter-regional correlations of D2 receptor binding were decomposed to assign numerical weights (path coefficients) to the anatomical connections. This computational method allows for the assessment of changes in the inter-regional associations of entire systems. It has been applied to the metabolic mapping data of functional brain imaging in which the model evaluated the influences on a relatively short (within minutes) time scale (Horwitz et al., 1995; Jennings et al., 1998a, b; Della-Maggiore et al., 2000; Goncalves et al., 2001). We applied this method to findings of regional receptor binding that could be assumed to influence each other and to change over the course of illness via the structural neuronal network. The strength and signs of these path coefficients were compared between groups and used to identify disease-specific changes in the connectivity of regional D2 receptor binding within the same anatomical network.

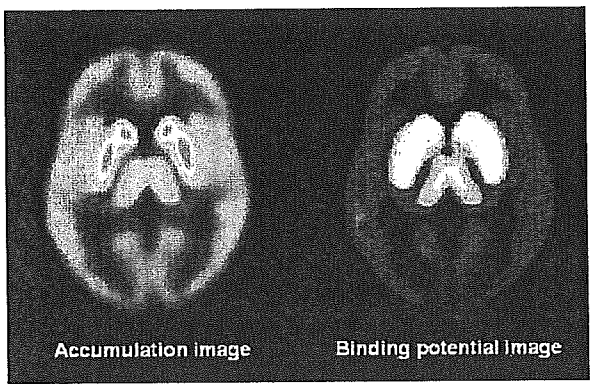

Fig. 1. Images of average accumulation of radioactivity and binding potential (BP) of [^{11}C]FLB 457 in normal controls (n=19). The individual images were anatomically standardized and averaged using Statistical Parametric Mapping (Friston et al., 1995). The images are at a level that includes the thalamus, anterior cingulate and fronto–temporal cortex. Colors show radioactivity and binding potential; red is high and purple is low. We could not evaluate BP in the striatum because of methodological problems and showed it as white blanks in the BP image.

2. Methods

2.1. Subjects

Ten drug-naïve male patients with schizophrenia (mean age=29.5, SD=7.8 years) who met DSM-IV criteria for schizophrenia or schizophreniform disorder were studied. Those with schizophreniform disorder at study entry met the criteria for schizophrenia at 6-month follow-up. Eight of the patients with individual MRI were the same as those reported in the previous study (Suhara et al., 2002), and two were newly recruited for this study with individual MRI. Three patients from the previous study were excluded because of the lack of MR images. The duration of illness ranged from 1 month to 7 years. Brief Psychiatric Rating Scale (BPRS) total scores ranged from 14 to 42 (mean=29.3, SD=8.9), with relatively higher scores for positive symptoms (mean=14.2, SD=4.0) than for negative symptoms (mean=5.5, SD=4.6) (Suhara et al., 2002). The control group comprised 19 age-matched healthy males (mean age=29.6, SD=7.5 years) who did not meet criteria for any neuropsychiatric disorder and who had no relatives with neuropsychiatric disorders. After explanation of the study, written informed consent was obtained from all patients and healthy subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET and MRI procedures

The ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA) was used to track radioactivity. The

system provides 63 planes and a 15.5-cm field of view (FOV). To minimize head movement, a head fixation device (Fixster, Stockholm, Sweden) was used. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Acquisitions were done in a three-dimensional mode with the interplane septa retracted. A bolus of 89.5–249.0 (mean=172.5, SD=40.0) MBq of [^{11}C]FLB 457 with high specific radioactivities (64.9–534.9 GBq/μmol) was injected intravenously into the antecubital vein with a 20-ml saline flush. This ligand was used because its high affinity provided sufficient signal-to-noise ratio in cortical and limbic regions with relatively low dopamine D_2 receptor density. Dynamic scans were performed for 80 min immediately after the injection. All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (full-width half-maximum=7.5 mm). The MR images were acquired on a Phillips Gyroscan NT, and 1.5-Tesla. T1-weighted images of the brain were obtained for all subjects. The scan parameters were 1-mm-thick three-dimensional T1 images with a transverse plane (TR/TE 19/10 ms, flip angle 30°, matrix 256×256, FOV 256 mm×256 mm, NEX 1).

2.3. Quantification of extrastriatal dopamine D2 receptors

Radioactivity in eight brain regions (anterior cingulate, thalamus, hippocampus, prefrontal cortex, temporal cortex and parietal cortex and midbrain/ventral tegmental area) was examined. A subset of these regions has been considered to be related to schizophrenic symptoms (Vollenweider, 1998). In this study we did not evaluate the striatal data because [^{11}C]FLB 457 is not a suitable ligand for quantitative analysis of the striatum (Farde et al., 1997; Suhara et al., 1999). Radioactivity of the cerebellum was also measured for the quantitative analysis. Radioactivity was derived from the mean of the voxel value within both right and left volumes of interest (VOIs) to increase the signal-to-noise ratio for the calculations and to simplify the assumptions and the model concerning the direction of influences and anatomy (Fig. 2).

Regional radioactivity of brain regions was obtained with a template-based method for defining VOIs as described in our recent article (Yasuno et al., 2002), with the exception of the midbrain/ventral

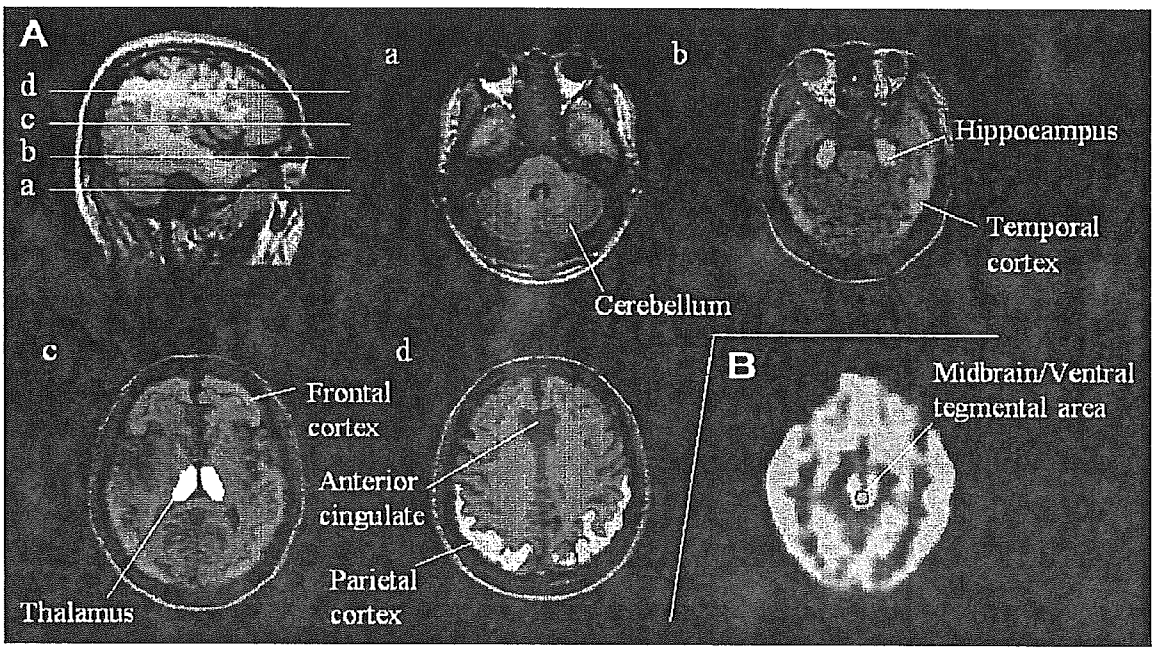

Fig. 2. (a) The transformed VOI template placed on the axial slices of an MRI of one subject after refining to a segmented gray matter image. The horizontal lines through the sagittal section indicate the point of intersection for each of the corresponding axial sections. (b) The manually delineated circular ROI overlying the midbrain area containing the raphe nuclei in the axial plane of summated PET images of one subject.

tegmental area. In short, the template-based method consisted of two major steps. The first step involved the spatial transformation of a template of a VOI from a model MRI to an individual MRI. The second step was to refine the transformed VOI to the individual segmented gray matter of the MRI using the intensity characteristics of these images. The finally refined VOIs were linearly transformed with the parameters obtained from the co-registration of the individual MRIs to PET images. The VOI on the midbrain/ventral tegmental area was defined as follows: a circular region of interest (ROI; 5-mm radius) was centered over the midbrain identified in the co-registered MRI where the ventral tegmental area was evident in the PET summation images.

The volume of the VOI defined on MR images was measured. The sizes of the area were summed across slices and multiplied by slice thickness (1 mm), yielding approximate volumes. The sizes [region (mean ± SD of control vs. patient)] were as follows: prefrontal cortex (16.0 ± 2.8 vs.15.8 ± 2.3 cm^3), temporal cortex (58.4 ± 4.5 vs. 59.9 ± 8.1 cm^3), parietal cortex (30.5 ± 5.1 vs. 28.5 ± 3.9 cm^3), thalamus (8.7 ± 1.6 vs.8.5 ± 1.1 cm^3), hippocampus (5.8 ± 0.8 vs. 5.1 ± 0.7 cm^3), anterior cingulate (4.7 ± 1.0 vs.4.6 ± 0.7 cm^3). The size of the midbrain/ventral tegmental area was the same among subjects (2.4 cm^3).

Quantitative tracer kinetic modeling was performed using a three-parameter (simplified) reference tissue compartmental model (Lammertsma and Hume, 1996). The cerebellum was used as reference tissue because it is nearly devoid of D2 receptors (Farde et al., 1997; Suhara et al., 1999). The model allows the estimation of binding potential (BP), which can be regarded as an index of receptor binding. BP is defined as follows; $BP=f_2B_{max}/\{K_d[1+\Sigma_i F_i/K_{di}]\}$, where f_2 is the "free fraction" of unbound radioligand, B_{max} is the density of receptor, K_d is the dissociation constant for the radioligand, and F_i and K_{di} are the free concentration and the dissociation constant of the competing endogenous ligand, respectively. We showed BP values of each VOI in Table 1. Group differences in BP values of the extrastriatal regions between patients and controls were compared using a two-tailed t test.

Table 1
Binding potential (BP) values for regions of interest[a]

Region		BP values	
		Controls ($n=19$)	Patients ($n=10$)
Prefrontal cortex	Right	1.07 ± 0.29	0.99 ± 0.15
	Left	1.04 ± 0.29	0.98 ± 0.16
	Right+left	1.05 ± 0.29	0.98 ± 0.15
Temporal cortex	Right	1.74 ± 0.30	1.70 ± 0.23
	Left	1.74 ± 0.30	1.83 ± 0.33
	Right+left	1.74 ± 0.30	1.75 ± 0.29
Parietal cortex	Right	1.20 ± 0.35	1.19 ± 0.19
	Left	1.18 ± 0.33	1.17 ± 0.23
	Right+left	1.19 ± 0.34	1.18 ± 0.21
Thalamus	Right	3.55 ± 0.55	3.32 ± 0.38
	Left	3.54 ± 0.51	3.30 ± 0.44
	Right+left	3.54 ± 0.45	3.30 ± 0.26
Hippocampus	Right	1.53 ± 0.44	1.46 ± 0.43
	Left	1.60 ± 0.41	1.52 ± 0.40
	Right+left	1.67 ± 0.34	1.49 ± 0.30
Anterior cingulate	–	1.17 ± 0.12	0.97 ± 0.17
Midbrain/ventral tegmentum	–	2.26 ± 0.44	2.37 ± 0.31

[a] Values are mean ± SD.

2.4. Network model analysis with structural equation modeling

The present study used structural equation modeling to evaluate the connectivity of regional D2 receptor binding in patients with schizophrenia and normal controls (McIntosh and Gonzalez-Lima, 1994; McIntosh et al., 1994; Horwitz et al., 1999). This computational method allows for the assessment of changes in the inter-regional associations of entire systems. When applied to neural systems, structural equation modeling combines information about anatomical pathways and the correlation coefficients of regional data between brain regions so as to identify the regional associations in a given condition. The correlations between areas are decomposed for assigning numerical weights (path coefficients) to anatomical connections, a process that produces a network model. The technical definition of a path coefficient (expressed in terms of neural pathways) is the direct proportional influence that one region has on another region through their direct anatomical connection, with all other regions in the model left unchanged. A path coefficient is the expected change in the activity of one region given a unit change in the region

influencing it (McIntosh and Gonzalez-Lima, 1994). In this study, the path coefficient indicates the relation of D2 receptors of one region to another through synaptic connections. Brain areas may associate with one another and compose a network with many regions, and large inter-regional covariances of any two regions can come about by not only direct but also indirect relations. Structural equation modeling describes the nature of inter-regional connections by expressing them as directional influences based on the hypothesis-generating model, and it can solve this interpretational problem for the correlations paradigm.

The inter-regional correlations of BP values and the anatomical model were combined using AMOS (version 4, SPSS, Inc.) to create structural equation models (Arbuckle and Wothke, 1995) that determined the path coefficients for each connection. We set the value of proportion of total variance in each region not accounted for by the effect of other regions. We fixed the values at 0.35–0.5 for a given brain region, and modified them if this improved the fit of the model (McIntosh and Gonzalez-Lima, 1994).

In the construction of the network model, we hypothesized that the dopaminergic system in the prefrontal cortex affected that of the anterior cingulate directly or indirectly via other cortical and limbic regions such as the thalamus or hippocampus, since the prefrontal cortex was thought to play some role in subcortical dopamine release in previous studies (Karreman and Moghaddam, 1996), and the anterior cingulate has direct neural input from the prefrontal cortex, temporo–parietal cortex (Vogt and Pandya, 1987), hippocampus (Tamminga et al., 2000) and thalamus (Vogt et al., 1987). Further, we also considered the connections from the midbrain/ventral tegmental area to other regions, since this area affects the limbic and cortical dopaminergic systems as the source of dopaminergic projections (Oades and Halliday, 1987).

In the first step of the construction, by the above hypothesis and the known neuroanatomy (Goldman-Rakic, 1987; Vollenweider, 1998; Steriade, 2001), we developed an initial network model in which it was decided that the path coefficient for feed-forward connectivity was from the prefrontal cortex to the anterior cingulate cortex directly, or indirectly via other cortical and limbic regions. Between the temporal and parietal cortex and the hippocampus and the thalamus, we applied reciprocal connections (Fig. 3a). In the next step, we included the path coefficients from the midbrain/ventral tegmental area to other regions (Fig. 3b), and in the last step, the influence of alternative path connections was estimated and included if it significantly improved the fit of the model with the chi-square statistics (Fig. 3c).

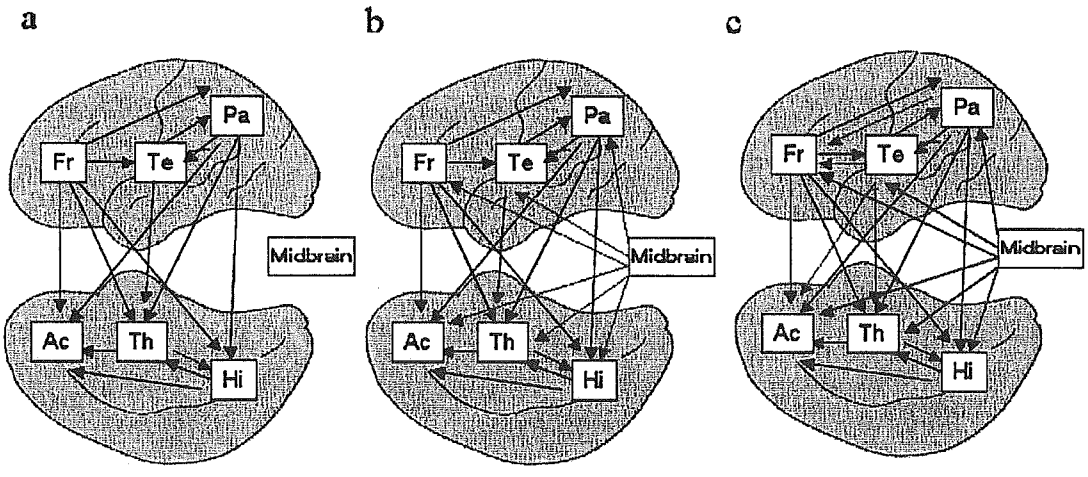

Fig. 3. (a) An initial network model developed under consideration of the known neuroanatomy, where it was decided to illustrate the path coefficients for feed-forward connections from the prefrontal cortex to the anterior cingulate via other cortical and limbic regions. (b) Modified model that included the connections from the midbrain/ventral tegmental area to other regions. (c) Test model in which the influence of alternative path connections was estimated and included if it significantly improved the fit of the model with the chi-square statistics. Red arrows indicated the added path connections to the initial and modified network models.