1. 論文発表

なし。

2. 学会発表

なし。

H. 知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

なし。

2. 実用新案登録

なし。

3. その他

なし。

Ⅲ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

【書籍】

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
東邦大学							
水野雅文.	早期診断・早期介入の意義と課題	水野雅文	専門医のための精神科臨床リュミエール5　統合失調症の早期診断と早期介入	中山書店	東京	2009	2-11
辻野尚久.	前駆期における薬物療法	水野雅文	専門医のための精神科臨床リュミエール5　統合失調症の早期診断と早期介入	中山書店	東京	2009	80-85
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IV. 研究成果の刊行物・別刷

専門医のための
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リュミエール
5

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統合失調症の早期診断と早期介入

【責任編集】水野雅文 東邦大学

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専門医のための精神科臨床リュミエール 5
統合失調症の早期診断と早期介入

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落丁・乱丁の場合はお取り替え致します.

Association between duration of untreated psychosis, premorbid functioning, and cognitive performance and the outcome of first-episode schizophrenia in Japanese patients: prospective study

Ryoko Yamazawa, Takahiro Nemoto, Hiroyuki Kobayashi, Bun Chino, Haruo Kashima, Masafumi Mizuno

Objective: The aim of the present study was to identify the relationship between duration of untreated psychosis (DUP), premorbid functioning, and cognitive dysfunction and the outcome of first-episode schizophrenia.
Method: Thirty-four neuroleptic-naïve patients who consulted hospitals in Tokyo and who were treated by psychiatrists for the first time were evaluated with regard to DUP, premorbid functioning, psychiatric symptoms, and global functioning. The neuropsychological test battery consisted of the Letter Cancellation Test, Trail-Making Test, Digit Span and Verbal Fluency Test. One year later, 24 of the subjects were reassessed for psychiatric symptoms, global functioning, and social functioning, and the relationships between DUP, premorbid functioning, and cognitive performance and the outcome was investigated.
Results: Short DUP, good premorbid functioning, and good Letter Cancellation Test, Digit Span and Verbal Fluency Test scores were significantly associated with good outcome.
Conclusions: The present results in a Japanese sample are consistent with previous international evidence that delay of initial treatment, premorbid functioning, and cognitive deficits are associated with outcome. A major limitation of the present study was the small size of the subject group. But because the subjects were relatively homogeneous and not influenced by psychoactive substances, the results reflect the essence of the disorder.
Key words: cognition, duration of untreated psychosis, first episode, premorbid functioning, schizophrenia.

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Schizophrenia is a heterogeneous disorder in terms of clinical presentation, pattern of response to medication, and long-term outcome. While some patients make relatively satisfactory progress, others experience a severe deteriorating course, and in the early stage of the illness it is very difficult to identify patients with characteristics that predict a poor long-term outcome. Predictors of treatment response and

long-term outcome are needed to offer appropriate intervention. The outcome predictive power of baseline characteristics has been investigated in several studies [1–6], and the results have shown that delay of initial treatment, negative symptoms [3,7,8], male gender [1,6,9–12], low education level [1,9], and poor premorbid adjustment are predictors of negative outcome.

Numerous studies that examined the relationship between duration of untreated psychosis (DUP) and outcome have been published, and most of them showed that longer DUP resulted in poorer outcome [13,14]. Based on this evidence a number of early intervention programmes have been developed around the world, and some reports have shown that such programmes shortened DUP and improved outcome [15,16].

These findings have drawn attention to the need for early intervention in first-episode psychosis. But psychiatric services in Japan are different from those in Western countries in several respects. The treatment of mental illness in Japan is hospital based, and there are a large number of psychiatric beds (28 beds per 10 000 population). The average length of hospital stay is 327.2 days, and 53.5% of inpatients have stays longer than 1 year. DUP in Japan, however, is similar (mean = 13.7 months) to that reported in studies abroad [17].

Great attention has recently been paid to cognitive dysfunction as a core feature of schizophrenia. A number of studies on cognitive deficits of first-episode schizophrenia have been carried out because the first episode of schizophrenia provides an optimal occasion to investigate the neurobiology of the disorder. This is because confounding factors such as hospitalization, long-term medication, and chronicity can be avoided. It has recently been said that cognitive deficits may occur even during the premorbid period, and impairments in attentional and executive performance, in particular, have been suggested as deficits that are evident many years before the onset of the first episode [18].

The present study focused on associations between DUP, premorbid functioning, and cognitive function and the outcome in a Japanese sample. Because few prospective studies of first-episode schizophrenia have been conducted in Japan, careful observation should provide valuable information in regard to the treatment of mental illness in Japan.

Methods

Subjects

Subjects were recruited from consecutive referrals to two hospitals in Tokyo between February 2001 and February 2003. All subjects met the ICD-10 criteria for schizophrenia and were treated by psychiatrists for the first time. The subjects fulfilled the following inclusion criteria: (i) age 16–44 years inclusive at the onset of the first episode; (ii) no history of psychiatric treatment; (iii) neuroleptic-naïve; (iv) not suffering from organic brain syndrome. None of the patients had a history of abuse of psychoactive substances including alcohol. Written informed consent was obtained after a complete description of the study was provided to the subjects and their relatives. This study complied with the ethical guidelines for research involving human participants as set out in the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Approval to collect data from medical records and informants was obtained from the ethics committees of the institutions involved.

Baseline assessment

Clinical assessment

We collected information from subjects, their family, and any other informant at the first consultation. Best-estimate age at onset based on all available information was used to determine DUP. We defined DUP as the interval between the onset of psychotic symptoms and the first prescription of neuroleptics for psychosis [17]. We identified the onset of psychotic symptoms as the time of first appearance of either (i) at least one of the first-rank symptoms of Schneider; or (ii) at least one of the four ICD-10 criteria in F20 (a–d). Negative symptoms and a reduction in social functioning were not considered in the assessment of DUP. We used the Premorbid Adjustment Scale (PAS) to assess premorbid functioning [19]. PAS yields measures of premorbid functioning in two different phases of life prior to the onset of illness: childhood (6–12 years) and adolescence and young adulthood (13–21 years). Higher scores indicate poorer premorbid functioning. Psychiatric symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) [20]. Global social functioning was measured on the Global Assessment of Functioning (GAF) [21]. The initial evaluation was performed within a few days after first consultation.

Neuropsychological assessment

The neuropsychological assessment was completed soon after subjects became able to cooperate with the tests. The neuropsychological test battery consisted of the following: (i) Letter Cancellation Test as a measure of visual search and attention [22]; (ii) Digit Span as a measure of immediate recall and verbal working memory [23]; (iii) Trail-Making Test as a measure of visuomotor sequencing involving connection of consecutive numbers randomly arranged on the page (part A) and of numbers and

letters in alternating order (part B) [24]; and (iv) Word Fluency Test (letter and category) as a measure of verbal fluency [25].

Outcome assessment

One year later the subjects were reassessed by means of the GAF, and the severity of psychiatric symptoms was assessed by means of the PANSS. At the same time we evaluated social functioning during the past 3 months by means of the Social Functioning Scale (SFS) [26]. The SFS is a self-report scale, and the subjects filled out a questionnaire. A higher score on the SFS indicates better social functioning.

Data analysis

All statistical analyses were performed using SPSS for Windows version 11 (SPSS, Chicago, IL, USA). Because a few subjects in all previous studies had an extremely long DUP, and they may have had an undue influence on the results, analyses based on raw DUP measurements involve various statistical difficulties. To avoid this problem the present subjects were divided into two groups according to the length of DUP, with the median DUP value as the dividing line. The Mann–Whitney U-test was used to assess differences between groups. Following Haas *et al.* [27] and Larsen *et al.* [28] we dichotomized the subjects on the basis of their PAS scores into a low-PAS group and a high-PAS group at the median value. Spearman's correlation analysis was used to examine the relationship between neuropsychological test score at first consultation and outcome.

Results

Sample characteristics

During the 2 year recruitment period 34 eligible patients agreed to take part in the study. None of the subjects had a lifetime history of any substance (including alcohol) abuse disorder. There were 10 dropouts between baseline and follow up. The dropouts were untraceable or had changed hospitals for geographical reasons, and one had committed suicide. There were no significant differences in demographic characteristics between those who completed the study and the dropouts.

The final sample consisted of 11 men (45.8%) and 13 women (54.2%), and their mean age was 27.0 years (SD = 6.57, range = 16–44). Ten of the 24 were inpatients at the time of the baseline assessment. Mean DUP was 8.3 months (SD = 13.42, range = 0.1–48), and the median DUP was 3 months. The demographic and clinical profiles of the subjects are shown in Table 1.

DUP and outcome

Table 2 shows the mean scores on the PANSS, GAF, and SFS of both the long-DUP group and short-DUP group. At follow up the negative symptom score of the short-DUP group was significantly better than that of the long-DUP group. The differences between the two groups in positive symptom score and GAF score were not significant.

Table 1. Subject characteristics

	Mean (SD)	Range
n (M/F)	24 (11/13)	
Age (years)	27.0 (6.6)	16–44
DUP (months)	8.3 (13.4)	0.1–48
PANSS (Positive)	24.8 (8.6)	9–42
(Negative)	23.3 (8.1)	11–39
(General)	46.2 (12.6)	27–67
GAF	30.5 (11.9)	15–55
PAS (6–12 years)	2.3 (2.1)	0–6
(13–21 years)	3.7 (2.8)	0–8

DUP, Duration of Untreated Psychosis; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.

Premorbid functioning and outcome

Table 3 shows the mean scores on the PANSS, GAF, and SFS of the low-PAS group and the high-PAS group. The PAS scores of childhood were associated with outcome: the scores on the PANSS (negative and general) and GAF in the low-PAS group were better than in the high-PAS group. But the results for the PAS scores of adolescence were not significantly associated with outcome.

Cognitive performance and outcome

The relationships between cognitive performance at baseline and clinical and social outcome are shown in Table 4. Significant correlations were found between attention and outcome: the lower the number of correct answers on the Letter Cancellation Test, the poorer the scores on the PANSS (general) and the GAF; the lower the number of correct answers on the Digit Span, the poorer the scores on the PANSS (negative) and the SFS. Moreover, significant

Table 2. DUP and outcome

	Short DUP Mean (SD)	Long DUP Mean (SD)
PANSS (Positive)	8.5 (2.1)	10.7 (4.3)
PANSS (Negative)*	12.8 (4.6)	18.9 (8.0)
PANSS (General)	25.1 (5.3)	32.3 (7.6)
GAF	69.5 (15.9)	59.2 (15.8)
SFS	128.8 (17.1)	107.9 (22.1)

DUP, Duration of Untreated Psychosis; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; SFS, Social Functioning Scale.; *$p < 0.05$.

Table 3. Premorbid functioning (PAS score) and outcome

	PAS (childhood)	
	Low	High
	Mean (SD)	Mean (SD)
PANSS (Positive)	7.8 (1.1)	10.5 (3.9)
PANSS (Negative)*	11.3 (2.9)	18.6 (6.1)
PANSS (General)**	24.3 (4.8)	32.3 (6.9)
GAF*	73.3 (10.9)	59.0 (15.6)
SFS	120.4 (23.8)	118.4 (22.8)
	PAS (adolescent)	
	Low	High
	Mean (SD)	Mean (SD)
PANSS (Positive)	7.9 (1.1)	10.2 (3.8)
PANSS (Negative)	13.3 (4.3)	17.8 (7.0)
PANSS (General)	26.9 (5.3)	31.9 (9.1)
GAF	69.4 (9.0)	59.1 (18.0)
SFS	117.9 (24.7)	120.4 (22.0)

GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; SFS, Social Functioning Scale.; *p <0.05, **p <0.01.

correlations were found between word fluency and outcome: the poorer the performance at the word fluency test (letter), the poorer score of the PANSS (positive, negative and general), and the GAF. No significant association was found between cognitive performance and SFS scores at follow up.

Discussion

The aim of the present study was to identify variables associated with the outcome of patients with first-episode schizophrenia in Japan, and DUP, premorbid function, attention, and verbal fluency were found to be associated with outcome.

DUP and outcome

A number of studies have reported a statistically significant relationship not only between DUP and outcome [2,3,5,12,29–37], but between DUP and time to treatment response [34,38]. These findings have provided support for the idea that intervention at or even before the onset of the first episode might improve response to treatment and long-term outcome. Lieberman *et al.* and Wyatt *et al.* hypothesized that untreated psychosis is biologically toxic [39,40], and Birchwood *et al.* suggested the critical period hypothesis, which suggested that deterioration occurs in the first 2–3 years of the illness, and that this deterioration might be arrested with appropriate and effective treatment [41]. DUP has also been found to influence long-term outcome in recent studies [9,42,43]. As a result numerous early detection and intervention programmes have been developed all over the world, and they have produced excellent results [13,15,16,44–47].

Perkins *et al.* reviewed the 43 reports on the association of DUP and treatment outcome and conducted a meta-analysis of the relationship [14]. The results of the meta-analysis showed that shorter DUP was associated with greater response to antipsychotic treatment, as measured by improvement or end-point severity of global psychopathology, positive symptom severity, and negative symptom severity, and the effect size for DUP and response for the combined statistic (all studies) was consistently significant.

In the present study the negative symptom score at follow up was better in the short-DUP group than in the long-DUP group, similar to the results of previous studies abroad. Our previous study showed a significantly longer duration of the first admission in the long-DUP group than in the short-DUP group.

Table 4. Neuropsychological scale scores and outcome (Spearman's coefficients)

			Follow up		
Baseline	PANSS-P	PANSS-N	PANSS-G	GAF	SFS
Letter Cancellation Test (correct)	–0.161	–0.416	–0.582**	0.458*	0.146
Letter Cancellation Test (Time)	0.343	0.349	0.415	–0.237	–0.330
Word Fluency Test (Letter)	–0.590*	–0.589*	–0.523*	0.567*	0.283
Word Fluency Test (Category)	–0.425	–0.272	–0.377	0.313	0.335
Trail-Making Test	–0.211	0.110	0.297	–0.313	0.207
Digit Span	0.206	–0.538*	–0.382	0.443	0.747**

G, General; GAF, Global Assessment of Functioning; N, Negative; P, Positive; PANSS, Positive and Negative Syndrome Scale; SFS, Social Functioning Scale.; *p <0.05, **p <0.01.

Thus, ameliorating the symptoms of the initial psychotic episode may not only lessen the immediate suffering experienced by patients and their relatives, but improve the long-term outcome by limiting progression of the disease and maintaining the patient's ability to respond to treatment.

Premorbid functioning and outcome

A number of studies have attempted to demonstrate an association between premorbid function and outcome, and PAS has been used most frequently to assess premorbid functioning.

Larsen *et al.* suggested that poor premorbid functioning was significantly correlated with more PANSS negative and general symptoms and poorer GAF score at 1 year [2]. Perkins *et al.* and Malla *et al.* reported that poor premorbid functioning was associated with poor outcome [5,12]. Hafner *et al.* reported that negative symptoms developed over a longer period even prior to the onset of the first psychotic episode and that early development of negative symptoms is likely to represent deficits in premorbid functioning [48]. Thus, premorbid functioning may be predictive of outcome. In the present study the PANSS (negative and general) and GAF scores at follow up were better in the low-PAS (childhood) group than in the high-PAS group. This finding was consistent with the results of previous studies. But in the present study the PAS scores for adolescence were not significantly correlated with outcome. Table 3 shows that the mean PANSS and GAF scores at follow up were better in the low-PAS adolescence group than in the high-PAS group. Although the differences were not statistically significant, they suggest that poor premorbid functioning at this age may be associated with poor outcome.

Cognitive performance and outcome

Cognitive dysfunction is considered a core feature of schizophrenia, and a number of studies that have assessed cognitive dysfunction in schizophrenia have been published. Because the subjects in many of the studies were chronic patients, the neuropsychological test scores may have been influenced not only by the severity of the illness itself but by long-term medication, duration of illness, and hospitalization. Cognitive function in first-episode schizophrenia with short duration of morbidity and medication has attracted the attention of many researchers as a means of understanding the essence of the cognitive dysfunction in schizophrenia. They have compared first-episode psychosis patients, chronic patients, and healthy control subjects on a comprehensive battery of neuropsychological tests to determine the degree of cognitive impairment [49–56]. These studies have shown that first-episode patients had larger generalized neuropsychological deficits than the healthy control subjects, and poor performance on measures of verbal learning and memory, attention, processing speed, and executive function. These findings suggested that cognitive deficits may be present at a very early stage in the course of the illness.

Some studies assessed neuropsychological performance as a possible predictor of outcome in first-episode psychotic patients [57–59]. Robinson *et al.* reported poor attention at baseline as well as male gender, obstetric complication, and severe hallucinations and delusions as variables associated with less likelihood of response to treatment [6]. Verdoux *et al.* reported that poor memory performance during the first admission was associated with risk of presenting with psychotic symptoms and rehospitalization at 2 year follow up [8]. Because some studies have reported an association between cognitive functioning and outcome [57,60,61], psychosocial interventions might potentially improve outcome.

In the present study attention and verbal fluency were found to be significantly associated with clinical outcome, consistent with the results of previous studies. None of the present subjects had a lifetime history of substance abuse or alcoholism. The present results, involving subjects who were relatively homogeneous and uninfluenced by psychoactive substances, reflect the true nature of the disorder itself. Cognitive deficits are considered a core feature of the disorder and reflect the vulnerability of patients to the disorder. Neuropsychological performance at the first consultation may enable prediction of the course and outcome.

It is also said that signs of cognitive deficits have been found to occur during the premorbid period and in early childhood. Caspi *et al.* assessed subjects' cognitive function as part of the Israeli Draft Board aptitude assessments at ages 16–17 when all were in good mental health, and again following manifestation of the first psychotic episode, and they compared their performance with that of healthy controls assessed at the same time [62]. No significant change in the patients with schizophrenia was found between the first and second assessment, and the schizophrenia patients performed worse than the controls on both the first and the second assessments. Some studies have reported that ultra-high-risk individuals had significant cognitive deficits [63]. Cannon *et al.*

suggested that neuropsychological performance, particularly attentional and executive deficits at 13 years of age, were related to adult psychiatric outcome [18], and assessing cognitive function in detail may therefore make it possible to predict the development of the first episode of psychosis.

In summary, the results of the present study in Japan are consistent with previous evidence in Western countries that delay of initial treatment, premorbid functioning, and cognitive deficits are associated with outcome. A major limitation of the present study was the small size of the subject population, which may limit the generalizability of the results. But because the subject group was relatively homogeneous and not influenced by psychoactive substances, the results reflect the essence of the disorder. Early detection and suitable intervention are regarded as important issues. The present results suggest that psychosocial interventions that shorten DUP and enhance cognitive function may be useful to improve outcome. In Japan the government has been making an effort to implement deinstitutionalization in recent years, although a little too late, and Japanese care for psychotic patients is behind the level of care in Western countries. The importance of early intervention and the factors associated with outcome were confirmed in this Japanese study, but further study to detect predictive factors not only of outcome but of the development to psychosis is needed.

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A self-reported instrument for prodromal symptoms of psychosis: Testing the clinical validity of the PRIME Screen—Revised (PS-R) in a Japanese population

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ABSTRACT

Objective: Early intervention for psychosis requires an easy, useful assessment instrument to identify subjects with prodromal symptoms at an early stage. The aim of this study was to test the clinical validity of the PRIME Screen—Revised (PS-R), a 12-item self-reported instrument for prodromal symptoms of psychosis, by comparing the results for a non-clinical population with those for a clinical population.

Method: The PS-R was administered to 1024 subjects (496 students and 528 outpatients). Of the 528 patients, 115 were randomly recruited and tested using the Structured Interview for Prodromal Syndromes (SIPS) to determine the concordant validity of the PS-R. The predictive validity of the PS-R was measured by determining the transition rate to psychosis during a 6-month follow-up period.

Results: The specificity and sensitivity of the PS-R, using the SIPS as a gold standard, were 0.74 and 1.00. The concordant validity of the PS-R against the SIPS was 0.43. The predictive validity of the PS-R and the SIPS, defined as the transition rate to psychosis, were 0.11 and 0.25, respectively. None of the patients with negative PS-R results developed psychosis.

Conclusions: Our findings showed that the PS-R was highly valid and that its usage is feasible in both general practice and clinical settings. This self-reported instrument represents a useful screening tool for alerting clinicians to subjects with psychotic prodromal symptoms.

1. Introduction

Several studies have shown that the prodromal phase of schizophrenia is characterized by attenuated psychotic symptoms, or psychotic-like experiences (PLEs) (Huber et al., 1980; Jackson et al., 1995; Yung and McGorry, 1996). Traditional assessment instruments were not sensitive enough to detect these subthreshold signs, and therefore a number of new instruments have been constructed (Klosterkötter et al., 1996; Yung et al., 2005; Miller et al., 2002). However, some interviews for these assessment instruments often take almost 1 h per patient, so they are not suitable for general practice and acute settings. In such settings, self-reported instruments showed a high validity, especially when administered to non-psychotic populations (Weiss et al., 1998; Winston et al.,

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2003). Based on these assessment instruments, some screening questionnaires have been developed (Heinimaa et al., 2003; Loewy et al., 2005).

The PRIME Screen, developed by Miller et al. at the PRIME clinic in New Haven, CT, USA, is one of these screening instruments (Miller et al., 2004). It is based on items from the Structured Interview for Prodromal Syndromes (SIPS), which was also developed by Miller et al. (2003). This screening questionnaire consists of 12 items covering positive symptoms and utilizes a self-rated scoring system of between 0 (definitely disagree) and 6 (definitely agree). In the developmental phase of the PRIME Screen, Miller et al. (2004) reported that it showed a sensitivity of 0.90 and had a perfect specificity, but these results were obtained using small samples ($n=36$) and the predictive validity was not examined. Moreover, the PRIME Screen was not validated in a non-clinical population.

Some studies have also revealed a high prevalence of attenuated psychotic symptoms or PLEs in non-clinical populations (Van Os et al., 2000). When other screening instruments were applied to the general population, their specificity was very low (Falloon, 1992; McGorry et al., 1995; Horneland et al., 2002). One of the reasons for the low specificity might be that most screening questionnaires are answered by a simple yes or no and are not concerned with the intensity or duration of the symptoms. The duration of prodromal symptoms is thought to be relatively long (3–5 years) (Häfner et al., 1992), and most of these symptoms were attenuated psychotic symptoms rather than brief limited intermittent psychotic symptoms (Miller et al., 2003; Yung et al., 1998). Those diagnosed as having a prodromal state, therefore, might have attenuated positive symptoms with a duration of more than one year. In view of the above points, we assumed that to improve the specificity of an initial screening, it would be more meaningful to examine the duration of the prodromal symptoms and to emphasize symptoms that lasted longer. Consequently, by adding a 'duration of symptoms' section to the PRIME Screen, we developed a new screening instrument, the PRIME Screen–Revised (PS-R); we then recalculated the cut-off criteria and examined the new instrument's clinical validity.

The new screening test comprises three types of clinical validities: clinical construct validity, concordant validity and predictive validity. The clinical construct validity shows that the screening test could sufficiently differentiate a clinical sample from a non-clinical population. The concordant validity demonstrates how far the result of the screening test coincides with the diagnoses based on the structured clinical interview that was conducted at baseline. The predictive validity refers to how long those who were positive on the screening test would be true positive during the follow-up period. The aim of this study was to assess the clinical validity of the PS-R by comparing help-seeking individuals to a non-clinical population and to assess the predictive validity of the PS-R using a large clinical sample.

2. Materials and methods

2.1. Subjects

We used two samples for testing the clinical construct validity of the PS-R: a non-help-seeking sample (students) and a help-seeking sample (outpatients). The non-help-seeking sample ($n=496$) was comprised of students from two universities (Aoyama-Gakuin University and Meiji-Gakuin University). We conducted the PS-R interview at the beginning of a class during the first week of a course in April 2005. All the participants gave their informed consent and had the right not to answer any question. Refusals per class were not documented, but the response rate suggests that the refusal rate was negligible. Both the Ethical Meeting of Aoyama-Gakuin University and the Meiji-Gakuin University's Institutional Review Board approved the study protocol and informed consent procedures in advance.

The help-seeking sample was comprised of psychiatric outpatients aged 16–30 years who first approached a community mental health clinic (Shakujii-Kouen Clinic, in a suburb of Tokyo) between July 2005 and November 2006. Five hundred twenty-eight of the 547 subjects (96.5%) agreed to participate and completed the PS-R, 4 (0.7%) declined to answer the questionnaire, and 15 (2.7%) could not understand the instructions or the meaning of the items. The study protocol and the informed consent procedures were approved by the Shakujii-Kouen Clinic's Institutional Review Board. All the participants were Japanese.

To test the concordant validity and predictive validity of the PS-R, we used a portion of the help-seeking sample. An interview that takes approximately 30–60 min to complete might be an unnecessary burden on non-help-seeking students and could cause a kind of stigma, creating ethical issues. Also, even the help-seeking patients did not always suffer from specific prodromal symptoms because community mental health clinics do not specialize in prodromal populations. Therefore, completing a full diagnostic interview with all of the non-help-seeking students and the first-visit patients was difficult. Consequently, to randomize the subjects, structured interviews were only conducted on one day of the week; patients who visited the clinic on the other days of the week were not interviewed.

Of the 528 outpatients who completed the PS-R, 119 (22.5%) were randomly recruited. Of the 119 patients, 2 patients who had an estimated IQ lower than 60 and 2 patients with substance abuse were excluded. We conducted further diagnostic interviews with the remaining 115 patients, after receiving their informed consents.

2.2. Measures

To evaluate the concordant validity of the PS-R, we used the SIPS as a gold standard. The Structured Clinical Interview for DSM-IV Axis I Disorder (SCID, First et al., 1997) was also administered, both to examine the predictive validity of the PS-R and to diagnose whether or not the subject was psychotic. The predictive validity of the PS-R was defined as the transition rate to psychosis for 6 months from the initial assessment. These diagnostic interviews (SIPS and SCID) were conducted by two experienced psychiatrists (H. Kobayashi and H. Koshikawa) and were rated independently from the PS-R.

The PS-R is a 12-item self-reported questionnaire that takes only a few minutes to complete. Eleven of the 12 items were chosen from among SIPS positive symptoms: unusual thought content, delusional ideas, suspiciousness, persecutory ideas, grandiose ideas, perceptual abnormalities, and hallucinations. The last item refers to loss of insight ('I have been concerned that I might be "going crazy".'), which was not derived from the

SIPS. The items of the PS-R were rated according to 7 degrees ranging from 0 (definitely disagree) to 6 (definitely agree), according to the SIPS rating scale. Moreover, we added items to the PRIME Screen asking how long the change in function, behavior or thought had been apparent such as less than 1 month, between 1 month and 1 year, more than 1 year). In other words, on the PS-R, all the items of the original PRIME Screen were used as they were, and only those items referring to the duration of the symptoms were added. The items of the PS-R are presented in the Appendix.

Previously, we translated the SIPS into Japanese and reported an excellent inter-rater reliability of the Japanese version (Kobayashi et al., 2006). We then translated the PRIME Screen and sent the back-translation to the original developer (T. Miller) to fine-tune the translation.

Using the original PRIME Screen criteria, subjects who selected more than one item with a rating of 6 (definitely agree) or more than three items with a rating of 5 (somewhat agree) were regarded as having tested positive (Tandy Miller, personal communication). However, this rating system, which assessed the intensity of the symptoms alone, did not take the duration of the symptoms into account. Therefore, we reset the cut-off criteria to reduce the false-positive rate. We classified the participants into 11 levels by mixing the severity of symptoms, the duration of symptoms and the total score of the PS-R (Table 1). To ensure a consistent screening test, the last item was excluded from the rating because only this item did not refer to attenuated positive symptoms. Therefore, the response to the 12th item of the original PRIME Screen was not taken into account when rating. Subjects with a rank of 4 or over were regarded as positive. After the exclusion of the 12th item, to receive a rank 4 or over the participant must have:

a) Selected one or more "definitely agree" response with a duration of more than one year or two or more "definitely agree" responses without regard to the duration,

or

b) Selected two or more "somewhat agree" responses with durations of more than one year,

or

c) Have a total PS-R score of 39 or over.

As for the total score, if the subjects selected "slightly agree" (score 4) for over half of the 11 items without regard to the duration (the total score would be 44), he or she was regarded as being 'at risk'. On the other hand, if the subjects selected "not sure" (score 3) for all of the items (the total score would be 33), he or she was regarded as not being 'at risk'. If the subjects selected "slightly agree" for half of the 11 items and "not sure" for the rest of the items, the total score theoretically would be 38.5. For this reason, we added criteria (c).

2.3. Statistical analyses

Subject characteristics measured as continuous variables were compared between groups by using Student's t test or Mann–Whitney U test. Chi-square tests or Fisher's exact tests were used to analyze categorical data. Multiple comparisons were conducted using univariate ANOVAs with Bonferroni's post hoc tests. All tests were two-tailed, and p values <0.05 were considered statistically significant. Data are expressed as means and standard deviations.

To examine the sensitivity and specificity of the PS-R, we used the receiver operator characteristics (ROC). ROC analysis was carried out using the non-parametric method of Hanley and McNeil (1982) to calculate, with 95% confidence limits, the area under the ROC curve (AUC). The AUC ranges from 0.5 (the discriminatory ability of a test is no better than chance) to 1.0 (perfect discriminatory ability). The difference of the AUC among methods was calculated with a z test (Hanley and McNeil, 1983). For the internal consistency of the PS-R, we calculated the Cronbach's α. Data were analyzed using SPSS version 11.0 for Windows (SPSS Inc., Chicago, USA) and MedCalc for Windows, version 9.3.9.0(MedCalc Software, Mariakerke, Belgium).

Table 1
Severity rank of the PS-R and the prevalence between two groups

Rank	Definition	Students		Outpatients	
		N	(%)	*n*	%
10	Selected three or more "definitely agree" responses with durations of more than one year	5	1	20	3.8
9	Selected two "definitely agree" responses with durations of more than one year	4	0.8	14	2.7
8	Selected two "definitely agree" responses with durations of more than one year or selected two or more "definitely agree" responses without regard to the duration and one or more "somewhat agree" response with a duration of more than one year	4	0.8	12	2.3
7	Selected one "definitely agree" response with a duration of more than one year *and* one or more "somewhat agree" response with a duration of more than one year	10	2	18	3.4
6	Selected two or more "definitely agree" responses without regard to the duration *or* selected three or more "somewhat agree" responses with durations of more than one year	5	1	38	7.2
5	selected one "definitely agree" response with a duration of more than one year *or* selected two "somewhat agree" response with durations of more than one year	18	3.6	37	7
4	Have a total PS-R score of 39 or over	3	0.6	6	1.1
3	Selected one "definitely agree" response without regard to the duration *or* selected one "somewhat agree" response with a duration of more than one year	40	8	72	13.7
2	Selected one or more "somewhat agree" response without regard to the duration *or* selected one or more "slightly agree" response with a duration of more than one year	65	13.1	81	15.4
1	Selected one or more "slightly agree" response without regard to the duration	66	13.3	48	9.1
0	Not selected any kind of "agree" response	276	55.6	180	34.2
Total		496	100	526*	100

* Not including 2 patients (ranks 9 and 5) who were diagnosed with psychosis at the beginning of the study.

3. Results

The demographic characteristics of the sample are presented in Table 2. As can be seen in the table, non-help-