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Ⅲ．　研究成果の刊行物・別刷

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Original Article

Clinical and social determinants of a longer duration of untreated psychosis of schizophrenia in a Japanese population

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Abstract

Aim: To measure the duration of untreated psychosis (DUP) among patients with schizophrenia in a Japanese population and to investigate clinical and social determinants of the DUP.

Methods: A multicentre, retrospective study at seven medical centres in three cities (Tokyo, Toyama and Kochi) was performed. In total, 150 consecutive patients (78 men) with neuroleptic-naïve first-episode schizophrenia were investigated; their DUP and demographic, clinical and social variables were obtained from their medical charts and analysed.

Results: The intraclass correlation coefficient for the DUP was quite good (ICC = 0.849). The mean DUP of all the subjects attending the seven psychiatric services was 20.3 months, and the median DUP was 6.0 months. Fourteen patients (9.3%) had a DUP of more than 60 months, and 47 patients, or about one-third, had a DUP of more than 24 months. No significant differences in the mean DUPs were observed among the three cities. Patients who were employed or who were students had a significantly shorter DUP (14.3 months). The median DUP for those with an insidious onset of psychosis ($n = 85$) was 18.0 months, compared with a median of 2.0 months for those with a sudden and acute onset ($n = 61$). However, no other clinical or social variables examined in this study were associated with differences in the DUP.

Conclusions: The DUP of patients with schizophrenia is relatively long in Japan. The provision and modification of psychiatric services for easy access and a system for the early recognition and detection of mental illness are needed.

Key words: DUP, early intervention, Japan, prevention, schizophrenia.

Numerous studies on the duration of untreated psychosis (DUP) have reported long average delays (often more than 1 or 2 years) from the onset of psychosis until the beginning of treatment. The DUP can also be influenced by various characteristics of the available psychiatric services. Two recent independent meta-analyses have provided substantial evidence that the DUP influences outcome.[1,2] The DUP is a substantial and promising quantitative index of public mental health in the sense that it can be used to compare psychiatric services in different countries and areas as well as contributing to policy-making and the future development of mental health service systems. Given the importance of DUP as a clinical measure and its implications for secondary prevention, the complicated methods of measuring this parameter should be addressed. DUP should be quantified in a simple and unified manner, and retrospective measurements should be possible, especially for large-scale samplings. However, Compton *et al.*[3] have commented that several limitations, including comparative assessments of the various measures and methods used to assess DUP, must be considered as the study of DUP progresses.

The DUP has also been used as a key variable in longitudinal studies,[4–8] but reports from countries with different attitudes towards psychiatric services are still rare, especially from East Asian countries; the DUP in Japan has been previously reported in a relatively small-scale study. Yamazawa *et al.*[9] reported a DUP of 13.7 months using data from one university medical centre and one psychiatric hospital in the Tokyo Metropolitan area, however, this study can by no means be regarded as representative of the situation in Japan. The specificity and differences in the Japanese psychiatric service system have been discussed elsewhere, but the main characteristics of the Japanese system are long hospital stays; a large number of psychiatric beds per unit population, of which more than 90% are located in private hospitals; and a very strong stigma associated with mental illness.[10] These circumstances make patient's access to psychiatric services difficult and complicate efforts to reduce the DUP. Nevertheless, shortening the DUP would reduce unnecessary suffering and may even reduce the direct negative consequences of psychotic episodes. To develop effective strategies for reducing the DUP, the factors contributing to treatment delay must be identified in each specific cultural background.

In this study, we investigated the DUP using data from seven medical centres located in three different areas of Japan. The present study focused on variations in the DUP among patients treated at different institutions and investigated its social determinants through which patients with first-episode psychosis had sought treatment in Japan.

METHOD

This multicentre, retrospective study investigated the DUP and related factors that may have contributed to a delay in the start of treatment. The data collection protocol, which was designed to respect the anonymity of each patient, was approved by the institutional ethical committees and complied with the ethical guidelines for epidemiological studies established by the Japanese Ministry of Health, Labour and Welfare.

The study was conducted in three areas of Japan over a two-year period; all the consecutive outpatients had been treated for a first episode of schizophrenia (conforming to ICD-10, code F20; World Health Organization, 1993)[11] at university hospitals or general hospitals with or without psychiatric beds between 1 April 2005 and 31 March 2007; such institutions may be more approachable than specialized hospitals. The institutions were located in the Tokyo Metropolitan area, Toyama City in Toyama Prefecture, and Kochi City in Kochi Prefecture. In the Tokyo Metropolitan area, three hospitals participated in the study: the Department of Neuropsychiatry at Toho University Medical Center Omori Hospital, located in downtown Tokyo with about 1000 beds, including 36 beds in the neuropsychiatry service; the Ohashi Hospital in central Tokyo, a general hospital with about 400 beds and no psychiatric beds; and Keio University Hospital, with about 1000 beds, including 31 beds in the neuropsychiatry service. Two hospitals from Toyama Prefecture participated in the study: the Department of Psychiatry at Toyama University Hospital, with 810 beds, including 80 psychiatric beds; and the psychiatric service of the Toyama Prefectural Hospital. Finally, two hospitals from Kochi Prefecture participated in the study: the Department of Psychiatry at Kochi University Hospital, with 605 beds, including 35 psychiatric beds; and the psychiatric service of the Kochi Red Cross Hospital.

Diagnoses were made according to the International Statistical Classification of Diseases and related Health Problems (ICD-10 criteria (WHO[11])) by the staff psychiatrist at the time of the patient's first visit to the hospital. The seven participating hospitals are all university teaching hospitals, and the consultation and diagnosis of the first-visit patients are made by the staff psychiatrists with more than 10 years experience in psychiatry, and the medical records are usually written by themselves. The diagnoses were then confirmed by two independent principal investigators at each centre using the information contained in each patient's medical records. When the three psychiatrists agreed unanimously that the diagnosis was schizophrenia (F20), the case was included in the present study. The age of the subjects in some previous DUP studies[7,9] was limited to between 15 and 55 years, and we adopted the same criteria for patient age.

Several methods have been used to measure DUP. We defined the DUP as the interval (in months) between the onset of psychotic symptoms and the first prescription of neuroleptics for psychosis. All the subjects were neuroleptic-naïve at the time of their first consultation. We defined the onset of schizophrenia as follows: (i) presence of at least one of the first-rank symptoms of Schneider,[12] 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 when assessing the DUP.

The main clinical and social variables of the subjects and family members were also noted and

analysed. The clinical variables included sex, onset age, age at first treatment for psychosis, severity of illness as rated by the Clinical Global Impression (CGI) score,[13] and the mode of onset. Data concerning the mode of onset was operationalized and rated according to the three main categories in the Personal and Psychiatric History Schedule (World Health Organization, 1996): (i) sudden (psychotic symptoms appeared within days of first noticeable behavioural changes); (ii) acute (psychotic symptoms appeared within one month of first noticeable behavioural changes); and (iii) insidious (psychotic symptoms appeared incrementally over a period of more than one month since the first noticeable behavioural change), following a recent AESOP study (Morgan *et al.*[14]). This procedure was based on how the mode of onset was defined in WHO studies examining the incidence and outcome of schizophrenia (Jablensky *et al.* 1992).[15]

The following social variables were assessed: presence of family members living together in the same residence, attendance of at least one of family members for the first consultation, social participation level at the time of the first consultation, and pathway through which the psychiatric services were accessed. 'Social participation' refers to attending school or having a non-sheltered job.

To confirm the inter-investigator reliability, 12 psychiatrists, two at least from each centre, participated in a reliability study. Twenty sets of medical records from two centres were presented independently, and the psychiatrists were asked to determine the DUP retrospectively by reviewing the first-rank symptoms and the ICD-10 criteria for schizophrenia described in the available clinical charts.

An unpaired *t*-test was used to compare differences between two groups. Because of the non-normal data distribution, the Mann–Whitney *U*-test was used for all the analyses. Significance levels were set at $P < 0.05$.

RESULTS

During the study period, 150 patients (72 women) who met the study criteria were identified from among all the cases treated at the seven psychiatric services. Medical records containing information sufficient to rate the DUP were available for all the cases.

Sample characteristics

The intraclass correlation coefficient on the DUP was quite good (single measure, ICC = 0.849).

The mean DUP (range) of all the subjects attending the seven psychiatric services was 20.3 (0–240) months; the mean DUP of the patients attending hospitals with psychiatric beds was 21.4 months, whereas that of patients attending hospitals without psychiatric beds was 16.7 months. The statistical differences among the mean ages of the patients attending each of the seven psychiatric services were not significant.

The median DUP of all the subjects attending the seven psychiatric services was 6.0 months (interquartile range: 2–25 months); the median DUP of patients attending hospitals with psychiatric beds was 7.0 months, whereas that of patients attending hospitals without psychiatric beds was 6.0 months.

Fourteen patients (9.3%) had a DUP of more than 60 months and forty-seven, about one-third had one of more than 24 months.

The average age at onset overall was 29.0 years (SD = 9.1 years); the average age of onset was significantly lower among men (mean, 27.0 years; SD = 7.6 years) than among women (mean, 31.2 years; SD = 10.3 years; $t = -2.867$, $P = 0.008$). Additional data is shown in Table 1.

No significant differences in the mean DUPs were observed among the three cities (Tokyo, Toyama, and Kochi) (Table 2).

Effects of living with others and social participation level

No significant difference between the DUP of subjects living alone (14.5 months) and that of subjects living with others (22.4 months) was observed. Patients who were employed or who were students, however, had a significantly shorter DUP (14.3 (24.0) months, SD in parentheses) than those who were unemployed (32.8 (42.2) months; $t = -2.79$, $P = 0.007$). The 113 patients who were accompanied by someone when they visited the hospital tended to have a shorter DUP (17.6 (31.1) months) than the 37 patients who came alone (28.4 (33.7) months), but the difference was not significant. However, the CGI scores of patients who were accompanied by someone were higher (4.46 (0.756)) than those of patients who came alone (4.05 (0.664); $t = -2.917$, $P = 0.004$).

The mode of onset and DUP

With the exception of employment, none of the demographic and clinical variables examined in this study were associated with differences in the DUP. However, large differences in the DUP were

TABLE 1. Clinical and social characteristics of entire patient sample

	Total sample (n = 150)	Mean DUP of each group (range)
DUP (in months)		
Median (IQR)	6.0 (2–25)	–
Mean (range)	20.3 (0–240)	–
Gender, n (%)		
Male	78 (52.0%)	18.9 (0–240)
Female	72 (48.0%)	21.9 (0–132)
Mean age at onset (in years)		
Male (SD)	27.0 (7.6)	–
Female (SD)	31.2 (10.3)	–
Living circumstances, n (%)		
Lives alone	35 (23.3%)	14.5 (0–132)
Lives with others	113 (75.3%)	22.4 (0–240)
Unknown	2 (1.3%)	–
Relationship status, n (%)		
Single	111 (74%)	20.7 (0–240)
In a stable relationship	39 (26%)	19.2 (0.25–120)
Education, n (%)		
Up to age 15 years	6 (4.0%)	26.8 (2–48)
Age 15–18 years	43 (28.7%)	20.9 (0.25–132)
Age 18–22 years	88 (58.7%)	21.4 (0–240)
Over age 22 years	6 (4.0%)	3.0 (0.2–12)
Unknown	7 (4.7%)	–
Employment status, n (%)		
Employed	95 (63.3%)	**14.3** (0–120)
Unemployed	48 (32.0%)	**32.8** (0.25–240)
Unknown	7 (4.7%)	–
Mode of onset, n (%)		
Sudden (<1 week)	3 (2.0%)	0.3 (0.1–0.5)
Acute (<1 month)	58 (38.7%)	5.6 (0–36)
Insidious (>1 month)	85 (56.7%)	29.2 (0.2–240)
Unknown	4 (2.7%)	–

The figures in bold represent statistically significant differences.
DUP, duration of untreated psychosis; IQR, interquartile range.

TABLE 2. DUP in three cities

	Tokyo	Toyama	Kochi
n (%)	109 (72.7%)	22 (14.7%)	19 (12.7%)
Median (IQR)	7.0 (2.5–24.5)	6.0 (1.0–25.5)	3.0 (1.0–30.0)
Mean (SD)	22.2 (35.2)	13.0 (15.2)	17.8 (23.5)

DUP, duration of untreated psychosis; IQR, interquartile range.

observed according to the mode of onset (Table 3). The median DUP for those with an insidious onset of psychosis (n = 85) was 18.0 months, compared with a median of 2.0 months for those with sudden and acute onset (n = 61; z = –6.463, P < 0.001; see Fig. 1).

Among the 85 cases with insidious onset, 52 patients (61.2%) had some kind of social participation at the time of their first visit to see a psychiatrist; 69 (81.2%) were living together with someone; and 57 (67.1%) were accompanied by someone at the time of their first visit. No significant differences in the mean age of onset or the age at first treatment of psychosis were observed between those with sudden and acute onset and those with insidious onset.

Pathways to psychiatric services

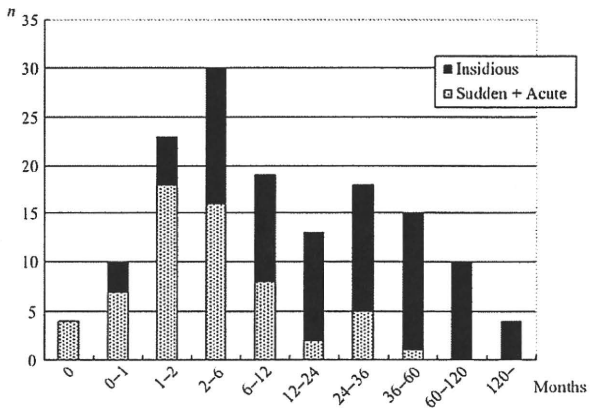
Fifty-two subjects (34.6%) decided by themselves to visit a psychiatric service; 46 subjects (30.6%) visited the psychiatric service acting on the recommendation of a family member living with the patient; and 34 (22.6%) were referred by outpatient clinic services. Only 11 patients (7.3%) were referred by a company clinic or were acting on the suggestion of a school nurse.

TABLE 3. Comparison of sudden or acute and insidious onset groups

	Sudden or acute (n = 61)	Insidious (n = 85)
DUP (in months)		
Mean (SD)	5.3 (7.7)	29.2 (36.6)
Median (range)	**2.0** (0–36)	**18.0** (0–240)
Gender n (%)		
Male	30 (49.2%)	47 (55.3%)
Female	31 (50.8%)	38 (44.7%)
Age		
Average (range)	30.8 (16–53)	30.4 (16–54)
Male (range)	27.4 (16–37)	29.4 (16–52)
Female (range)	34.1 (17–53)	31.6 (16–54)
Mean age at onset		
Average (range)	30.5 (16–52)	28.0 (15–54)
Male (range)	27.0 (16–37)	27.1 (15–48)
Female (range)	33.8 (17–52)	29.1 (15–54)
Living circumstances, n (%)		
Lives alone	19 (31.1%)	16 (18.8%)
Lives with others	41 (67.2%)	69 (81.2%)
Relationship status, n (%)		
Single	43 (70.5%)	65 (76.5%)
In a stable relationship	18 (29.5%)	20 (23.5%)
Education, n (%)		
Up to age 15 years	2 (3.3%)	4 (4.7%)
Age 15–18 years	13 (21.3%)	29 (34.1%)
Age 18–22 years	39 (64.9%)	46 (54.1%)
Over age 22 years	3 (4.9%)	3 (3.5%)
Unknown	4 (6.6%)	3 (3.5%)
Employment status, n (%)		
Unemployed	15 (24.6%)	29 (34.1%)
Others	43 (70.5%)	52 (61.2%)
Unknown	3 (4.9%)	4 (4.7%)

The figures in bold represent statistically significant differences.
DUP, duration of untreated psychosis.

FIGURE 1. Histogram of duration of untreated psychosis and numbers of cases. Insidious, insidious mode of onset group. Sudden + Acute, sudden and acute mode of onset group.



DISCUSSION

First of all, the DUP in Japan is relatively long, even though the patients included in the study are only a subset of all patients who developed a first episode during the study period in the study area and the selection bias could not be neglected. Japan is a developed country with rich medical resources including a public insurance system for all citizens.

The data in this study were collected from people who sought help at general or university hospitals located in an urban area. The mean DUP in this study (20.3 months) was longer than the previously reported value of 13.7 months for a study conducted in 2000 in Tokyo, Japan.[9] The DUP would likely be even longer if data from specialized psychiatric hospitals were to be included, especially those in rural areas, where a large stigma against mental illness exists.

Although retrospective studies have some inherent limitations including less precise DUP measurement in months, not in weeks, the ICC was very high in this study and the data were thought to be sufficiently reliable. The high ICC among the psychiatrists was also notable. In this study, the DUP was determined by checking the medical charts of each patient written by the treating psychiatrists; nevertheless, the ICC was quite high. When the investigators were asked to determine the DUPs retrospectively based on the patients' medical records, the investigators noted the description of the onset episode and confirmed the date of the first consultation. Naturally, the high ICC between psychiatrists simply means that they all came to the same conclusion on the basis of what was written in the files, and it does not prove that the conclusion is correct in terms of what the DUP actually was. However, vice versa, as the doctors were very thorough when they were writing the medical records; therefore, the investigators were able to reach unanimous decisions regarding the DUPs.

One serious problem revealed by this study is that about one-third of the patients visited a psychiatrist for the first time after more than 24 months had passed since the initial onset of their condition; in other words, their DUP was longer than two years, which is regarded as a critical period when long-term treatment resistance is apparent (Birchwood *et al.*[16]). The importance of this critical period with regard to a favourable outcome has recently been emphasized. de Haan *et al.* (2002)[17] has pointed out that some awareness of mental disorder at onset was related to a shorter DUP.

As Morgan *et al.* (2006)[14] have pointed out and as Compton *et al.* (2008)[18] have confirmed, the mode

of onset is a very important factor for distinguishing the length of DUP, and an insidious mode of onset was associated with a substantially longer DUP, compared with an acute onset. In our study, however, many of the patients with an acute mode of onset also experienced a long DUP as shown in Fig. 1, whereas a number of people with an insidious onset had a relatively short DUP. Further analysis of the reasons why some people with an insidious mode of onset exhibited help-seeking behaviour after a shorter untreated period may suggest methods for shortening the DUP. Psychopathological analysis of initial positive symptoms or subjective experiences during the early stage of disease may answer these questions.

Patients and families can be reluctant to seek help for a variety of reasons, such as poor knowledge of the features of mental disorders and their treatability, beliefs that the problem can be solved without help, the stigma and shame associated with mental illness, and a desire to confine the problem within existing networks.[19] In Asian countries, which often have a strong stigma against mental illness, family relations should also be taken into consideration.[20]

To identify the reasons for the relatively long DUP in Japan, public attitudes towards psychosis, mental illness and the people with these diseases should be investigated. However, a recent review on public beliefs and attitudes towards people with mental disorders could only conclude that little is known about the relation between attitudes towards people with mental disorders and the actual behaviour towards them. According to Angermeyer *et al.* (2006),[21] most of these types of studies have been performed in Europe, and there have been some indications of inter-cultural variations in beliefs and attitudes.

Jorm *et al.* (2005)[22] investigated public beliefs regarding mental disorders and compared the Japanese and Australian people. According to their survey, the Japanese were more reluctant to discuss mental disorders with others outside the family. They generally believed in the benefits of treatment but were not optimistic regarding a full recovery. In contrast, Australians were more positive about the benefits of seeking professional help but had a strong preference for lifestyle interventions and tended to have negative responses towards the use of some psychiatric medications.[22] Such tendencies might explain the longer DUP observed for patients living with family members in Japan.

In the present study, 22.6% of the patients were referred by outpatient psychiatric services, whereas 65.2% came to the hospitals based on their own decision or accompanied by a family member. A previous study from Japan by Yamazawa showed that none of the subjects were referred to the psychiatric services by so-called general practitioners (GPs), and the authors concluded that GPs were not contributing to the early detection of mental illness in Japan. The general practitioner system does not exist in Japan, and certification as a specialist in primary care is not available. Family practitioners with offices in the community provide primary care for patients as 'general practitioners', but they are not specialists in primary care. Instead, they have been trained in other specialties, such as internal medicine, paediatrics or surgery. However, in Japan, about half of the patients who experienced an initial episode of mental disorder had consulted a GP or an internist at a general hospital before consulting a psychiatrist (Koizumi, 2007).[23] However, the authors reported that almost half of the patients who had experienced a first episode of mental illness were told nothing of their diagnosis or their mental condition by these GPs or physicians at general hospitals. Unfortunately, family physicians in Japan do not perform screening for the early detection of mental illness in Japan. The provision and modification of psychiatric services for easy access and a system for the early recognition and detection of mental illness are needed in Japan, rather than increasing the number of psychiatry clinics. On the other hand, it is interesting that Norman *et al.* (2004)[24] also insist the education of service providers to recognize psychosis, identifying the increased DUP of patients followed by family physicians/GPs in a Canadian sample.

The above results highlight the importance of further education for GPs about mental disorders to provide early and appropriate care for patients and to change prevailing attitudes regarding schizophrenia.

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Perspectives in Early Intervention

Correlation between attenuated psychotic experiences and depressive symptoms among Japanese students

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Abstract

Aims: To examine the emergence of attenuated psychotic experiences, self-disturbance or affective symptoms among younger subjects in the general population and to investigate the intergroup differences on each symptom between adolescents and post-adolescents.

Methods: A total of 781 participants, 496 university students (mean age: 19.3 ± 1.1 years) and 285 high school students (mean age: 16.0 ± 0.3 years), were administered self-reported questionnaires. Psychotic prodromal symptoms were evaluated using the PRIME Screen-Revised (PS-R), a 12-item self-reported questionnaire. To measure the cognitive, emotional and physical symptoms associated with depression, the Zung Self-rating Depression Scale (ZSDS), a 20-item self-reported questionnaire, was administered.

Results: There were no intergroup differences on the factor score of the PS-R, except the self-demarcation factor (post-adolescents > adolescents), whereas there were significant differences in the factor score of the ZSDS, except for the anxiety factor. Among the post-adolescents, the factors of the PS-R showed a moderate correlation to the cognitive factor on the ZSDS; among the adolescents, the PS-R factors showed a greater correlation to the anxiety factor on the ZSDS than other factors. There were no differences in the distribution of each item of the PS-R between the two groups.

Conclusions: The disturbance of self results in difficulty to precisely objectify, especially among adolescents, which would induce more primitive reactions such as agitation, irritability or anxiety; probably, the self disturbance would become an explicit symptom from an implicit experience with advancing age of the subject. Although these data are only preliminary, they could explain the pathway of progression prior to the onset of psychosis, from disturbance within the self to exaggerated self-absorption.

Key words: depression, prodromal symptom, prodrome, psychosis, ultra-high-risk.

INTRODUCTION

Recent studies on the early phase of psychotic disorders have shown a characteristic clinical picture prior to the onset of psychosis.[1,2] They have indicated that most individuals at risk of psychosis experience attenuated psychotic symptoms, and that this would be clinically relevant to detect such attenuated symptoms or psychotic-like experiences (PLEs) for identifying patients at a high risk of developing psychosis.[3,4] Indeed, current criteria for the 'ultra high risk' (UHR) state[5,6] are largely based on the presence of PLEs, which seems to be widely accepted.

However, several population-based studies have also revealed that some PLEs are not uncommon

and may not necessitate the seeking of help.[7,8] Therefore, those who are identified as 'positive' cases by the PLEs-based criteria may include a significant number of 'false positive' cases, who are not actually at a risk of psychosis at all. Yung *et al.* suggested that the detection of PLEs only may not be a valid method to identify a UHR sample, especially in the general population.[9]

Recent focus on the self-disturbance and affective symptoms during the prodromal phase[10,11] might shed a new perspective on this 'false positive' issue. Thus far, a few prospective studies indicate that the disturbances of self are specific to the schizophrenia spectrum disorders and mark the prodromal phase. Hartmann *et al.* revealed that fluidity of self-demarcation, lack of a coherent narrative-historical self-identity and other self-disturbances could be considered as prominent features of preschizophrenic states at school age.[12] Klosterkötter *et al.* demonstrated that varieties of depersonalization, disturbances of the stream of consciousness and distorted bodily experiences could be precursors of later onset of schizophrenia.[13] Overall, these 'first-person dimensions' of the illness should be more fully reviewed,[14] and therefore, we aimed to explore these phenomenological changes of the self in the general population.

Affective disturbance such as depressive symptoms has been suggested to frequently mark the onset of the initial prodrome of psychosis. Depression has been found to be a significant predictor of psychosis in UHR groups.[15] Especially close to the time of onset of psychosis, individuals have displayed heightened emotionality.[16] In addition, as for identifying of persons subjecting from a potential prodrome, Schultze-Lutter *et al.* stated that it might be of importance to evaluate current affective status.[11] Thus, we assumed that the disturbance of self during the prodromal phase might be associated with affective disturbance and considered it necessary to examine the correlations between the self disturbance and affective symptoms in youth in the general population.

A recent study showed that younger age was significantly associated with endorsement of PLEs.[17] This age-related decline in the prevalence of PLEs may reflect the developmental trajectory of PLEs.[18] Van Os and his colleagues have proposed that PLEs that persist into post-adolescent may be a reflection of delayed neurophysiological maturation.[19] Given these assumptions, there would be some differences in the type of PLEs between adolescents and post-adolescents. Our hypothesis is that adolescents present with less specific and less differentiated symptoms, such as anxiety or affective reaction, than post-adolescents.

Similarly, administering the self-reported questionnaires to adolescents may be controversial, partly because their validity or reliability may be unclear when used for adolescents. However, several studies have noted that adolescents rarely confide PLEs to caregivers or clinicians[20,21] and that the self-report measure used for adolescents was more informative than other measures completed by someone else.[18] Our previous study also showed that a self-reporting instrument for the subjective experiences of individuals with an at-risk mental state (PRIME Screen-Revised) could be reliable;[22] disturbance of self could thus be detected through a self-reported questionnaire.

The aims of this study were to examine the emergence of attenuated psychotic experiences, self disturbance or affective symptoms among younger subjects in the general population and to investigate the intergroup differences on each symptom between adolescents (high school students) and post-adolescents (university students) using the self-reported questionnaire.

METHOD

Participants

The subjects comprised the students of two universities and two high schools. A total of 781 (496 university students and 285 high school students) participants were administered the self-reported questionnaire without any advance information on the history of psychiatric disorders or related symptoms. All the participants gave their informed consent and were explained the right to not answer/answer any question. Of the 781 students, 762 (97.6%) completed the questionnaires, four (0.7%) declined to answer the questionnaires and 15 (2.7%) could not understand the instructions or the meaning of the questions. Either the ethics meeting or the Institutional Review Board at the universities/high schools approved of the study protocol and of the informed consent procedures. All the participants were Japanese subjects.

Measures

PRIME Screen-Revised

The original PRIME Screen, developed by Miller *et al.* at the PRIME clinic in New Haven, CT, USA, is one of the screening instruments for the risk of

psychosis.[23] It is based on items from the Structured Interview for Prodromal Syndromes (SIPS), which was also developed by Miller *et al.*[6] This screening questionnaire consists of 12 items covering positive symptoms (unusual thought content, delusional ideas, suspiciousness, persecutory ideas, grandiose ideas, perceptual abnormalities and hallucinations) and a self-rating between 0 (definitely disagree) and 6 (definitely agree). Based on this original PRIME Screen, we developed the PRIME Screen-Revised (PS-R), by adding the question to the PRIME Screen that asked how long the change in function, behaviour or thought had been apparent (such as less than 1 week, between 1 week and 1 year, more than 1 year). Given that the duration of prodromal symptoms was relatively long (3–5 years)[24] and most of these symptoms were attenuated psychotic symptoms rather than brief limited intermittent psychotic symptoms,[3,6] we speculated that those who are diagnosed as prodromal state might have attenuated positive symptoms with more than 1-year duration. Thus, we assumed that for better specificity of initial screening, it would be more meaningful to examine the extent to which prodromal symptoms continued and to make much of symptoms which last longer, and therefore, we added 'duration of symptoms' sections to the PRIME Screen and reset the cut-off criteria. The last item of the PS-R refers to loss of insight ('I have been concerned that I might be "going crazy"'), which was not derived from the SIPS and was not related to attenuated positive symptoms; therefore, the response to the 12th item was not taken into account at the time of the rating. The participants were classified into 11 ranks based on a combination of the severity of symptoms, the duration of symptoms and the total score on the PS-R. We had tested the clinical validity of the PS-R by comparing non-clinical population (496 students) to clinical population (528 outpatients).[22] If the subjects with a rank of 4 or over were regarded as positive, specificity and sensitivity of the PS-R using the SIPS as a gold standard were 0.74 and 1.00. Concordant validity between the PS-R and the SIPS was 0.43.[22] Thus, in this study, we categorized subjects with a rank of 4 or over as positive.

Previously, we had reported the results of a factor analysis of the PS-R in a sample including both clinical and non-clinical subjects (Kobayashi H, 2008, unpublished data). Four factors, namely self-demarcation, presence of self, grandiosity and stream of consciousness were extracted. These factors accounted for 70.1% of the variance on the PS-R. In this study, we examined the composition of these four factors.

Zung Self-rating Depression Scale

The Zung Self-rating Depression Scale (ZSDS), a 20-item self-reported questionnaire, was developed to measure the cognitive, emotional and physical symptoms associated with depression.[25] The items were rated on a 4-point Likert scale ranging from 1 (rarely) to 4 (most of the time), with higher scores corresponding to a greater severity of depressive symptomatology. The ZSDS has been established as a valid, reliable measure of depression in several studies and the factor structure of the ZSDS has been studied in different populations.[26] In this study, we used the four dimensions (core depressive, cognitive, anxiety and somatic) reported recently by Romera *et al.* from the factor analysis study in a large sample of patients in the primary care setting,[27] because our sample was clearly heterogeneous both in terms of age and help seeking.

Statistical analyses

Subject characteristics measured as continuous variables were compared between groups by Student's *t*-test or Mann–Whitney's *U*-test. Chi-squared tests or Fisher's exact tests were used to analyse categorical data. Associations between factors of the PS-R and ZSDS were analysed by calculating Spearman's rank correlations. All tests were two-tailed, and *P*-values of <0.05 were considered to be statistically significant. Data were expressed as means ± standard deviations. Data were analysed using SPSS, version 11.0, for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The high school students showed a significantly higher positive result rate of the PS-R than the university students, although the university students showed significantly higher total PS-R scores (Table 1). As Table 2 showed, however, there were no differences in the distribution of each item of the PS-R between the two groups.

There were no intergroup differences on the factor score of the PS-R, except factor 1 (self-demarcation), whereas there were significant differences in the factor score of the ZSDS, except for factor 3 (anxiety) (Table 1). In regard to the correlation between each of the items on the PS-R and ZSDS, there were some differences in the intensity of the correlations between the two groups. Among the university students, the factors of the PS-R showed a moderate correlation to the cognitive

TABLE 1. Sample characteristics

	High school students		University students		Significance
N	285		496		
Female (%)	152 (53.3)		303 (61.2)		n.s.
	Mean	SD	Mean	SD	
Age	16.0	0.3	19.3	1.1	
PS-R					
Self demarcation	4.9	5.3	5.9	4.9	$P < 0.05$
Presence of self	2.1	2.7	2.1	2.4	n.s.
Grandiosity	1.8	2.6	1.9	2.3	n.s.
Stream of consciousness	1.8	2.8	1.8	2.3	n.s.
Total score	12.9	13.0	14.5	11.8	$P < 0.01$
ZSDS					
Core depressive	18.2	4.6	15.4	4.1	$P < 0.01$
Cognitive	10.4	2.7	9.2	2.5	$P < 0.01$
Anxiety	5.4	2.0	5.5	2.0	n.s.
Somatic	4.4	1.8	4.7	1.4	$P < 0.01$
Total score	43.4	8.2	41.0	7.5	$P < 0.01$
	n	%	n	%	
PS-R positive rate (%)	36	14.6	46	9.3	$P < 0.01$

Note: PS-R, PRIME Screen-Revised; ZSDS, Zung Self-rating Depression Scale.

TABLE 2. Factors of the PRIME Screen-Revised and the prevalence of those endorsed the score of 4 or more

Factors and items	High school students	University students
Factor 1 – self demarcation	%	%
Telepathy-like experience I have thought that it might be possible that other people can read my mind, or that I can read other's minds	28.4	23.6
Ideas of reference I wonder if people may be planning to hurt me or even may be about to hurt me.	13.2	14.6
Ideas of passivity I may have felt that there could possibly be something interrupting or controlling my thoughts, feelings, or actions.	13.0	13.2
Perceptional distortions I think I might feel like my mind is 'playing tricks' on me.	6.1	5.3
Factor 2 – presence of self		
Derealization I think that I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams.	14.0	13.1
Delusional mood I think that I have felt that there are odd or unusual things going on that I can't explain.	6.3	8.5
Factor 3 – grandiosity		
Overvalued belief I think that I might be able to predict the future.	5.7	6.5
Increased self-esteem I believe that I have special natural or supernatural gifts beyond my talents and natural strengths.	7.7	7.8
Factor 4 – stream of consciousness		
Any auditory hallucinations I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me.	9.3	10.2
Thought hearing I think that I may hear my own thoughts being said out loud.	7.5	8.9
None		
Magical thinking I have had the experience of doing something differently because of my superstitions.	10	9.9

factor on the ZSDS; in the high school student, the PS-R factors showed a greater correlation to the anxiety factor on the ZSDS than other factors (Table 3).

When comparing the ZSDS total score in the PS-R positive versus negative subjects in the university students, significantly higher mean scores were observed in the PS-R-positive cases (44.5 ± 8.7 vs. 40.7 ± 7.3, $P < 0.01$), whereas no significant difference in the total ZSDS score was observed between the positive and negative cases on the PS-R in the high school students (44.8 ± 9.9 vs. 43.0 ± 7.7,

TABLE 3. Correlation coefficient between the factors of PS-R and ZSDS among high school and university students

	ZSDS				
	Core depressive	Cognitive	Anxiety	Somatic	ZSDS total score
PS-R (high school students)					
Self-demarcation	0.163*	0.119	**0.272****	0.101	0.180*
Presence of self	0.190**	0.154*	**0.331****	0.133*	**0.230****
Grandiosity	0.185**	−0.100	0.132*	0.098	−0.147
Stream of consciousness	0.130*	0.049	**0.207****	0.079	0.110
PS-R total score	0.080	0.023	**0.246****	0.081	0.176*
PS-R (university students)					
Self-demarcation	0.154**	**0.257****	0.158**	0.075	**0.290****
Presence of self	**0.225****	**0.245****	**0.229****	0.135**	**0.340****
Grandiosity	0.034	0.119**	−0.006	0.042	0.050
Stream of consciousness	0.109*	**0.250****	0.123**	0.013	**0.215****
PS-R total score	0.174**	**0.284****	**0.204****	0.128*	**0.304****

Note: Correlation coefficient of 0.20 or more are highlighted and in bold.
*$P < 0.05$; **$P < 0.01$.
PS-R, PRIME Screen-Revised; ZSDS, Zung Self-rating Depression Scale.

$P = 0.286$). There was no significant difference between males and females for the total score of both the PS-R and ZSDS (PS-R: $Z = -0.74$, $P > 0.05$, ZSDS: $Z = 1.31$, $P > 0.05$).

DISCUSSION

Our findings suggest that there are some differences in the type of subjective experiences between adolescents and post-adolescents. Among high school students, or adolescents, a greater correlation between attenuated psychotic experiences and the factor interpretable as anxiety (psychomotor agitation, irritability and sleep disturbance) than other factors was observed. On the other hand, among university students, or post-adolescents, there was a moderate correlation between the PS-R factors and the cognitive factor on the ZSDS: psychomotor retardation, confusion, indecisiveness or fatigue. Our results provide support for the hypothesis that the 'prodromal' changes at an earlier age still remain unaffected. The disturbance of self results in difficulty to precisely objectify, especially among adolescents, which would induce more primitive reactions such as agitation, irritability or anxiety. This could explain, at least in part, the relationship between PLEs and activation or maladaptation among adolescents.[28,29] Probably, the self-disturbance would become an explicit symptom from an implicit experience with advancing age of the subject.

However, there were no intergroup differences on the factor scores of the PS-R, except factor 1, self-demarcation as passivity phenomena, telepathy-like experiences, perceptual distortion or persecutory ideas. Fluidity of self-demarcation reflects the difficulties in distinguishing self from not-self and represents confusion with others, such that a subject loses sense of whose thoughts, feelings, or expressions originated in whom.[10] These subtle transitivistic phenomena are often expressed as a sense of being passive or at the mercy of the world, which might cause interpersonal difficulties or social isolation.[30] Although these data are only preliminary, they could explain the pathway of progression prior to the onset of psychosis, from disturbance within the self to exaggerated self-absorption.

Overall, attenuated psychotic experiences or self-disturbances showed a correlation to depressive symptoms, which is consistent with the other findings. Yung *et al.* reported that persecutory ideas and bizarre experiences were likely to be associated with distress, depression and poor functioning among non-psychotic help seekers.[29] Schultz-Lutter *et al.* found that 38% of potential prodromal subjects met the criteria for a current depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV, The American Psychiatric Association, 1994).[11] The degree to which depressive symptom has an impact on the development of psychosis is unclear but warrants examination.

This study also had limitations. The difficulty in objectifying the disturbance of self would also generate a false-positive issue. Our results indicate that a higher positive rate of PS-R was seen in the younger population, which could both be a reflection of the adolescent crisis and inclusion of a considerable number of false-positive cases. In addition, although discussed in the Introduction, younger subjects

may have misinterpreted questions and endorsed symptom items incorrectly, which may result in not only false-positive cases, but also false-negative cases. It is a methodological weakness that the subjective experiences were assessed only by a self-reported measure. Some subjects may conceal their anomalous experiences because of some incorrect beliefs or biases against psychiatric care. Additionally, the conclusions regarding self-disturbance would be strengthened if a direct measure of self-disturbance, for example, the EASE questionnaire[31] or basic symptoms questionnaires, had been used. Future studies on larger samples, including help-seeking subjects, and additional assessment by an interview could help clarify the relationship between attenuated psychotic experiences and depressive symptoms, and detect disturbance of the self specific to the prodromal state.

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Reduced prefrontal cortex activation during divergent thinking in schizophrenia: A multi-channel NIRS study

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ABSTRACT

Relationships between deficits in verbal fluency and poor social functioning have been revealed in patients with schizophrenia. In previous studies, we demonstrated that deficits in idea fluency, which is ranked as a more complex type of verbal fluency and reflects divergent thinking ability, were more closely related to social dysfunction than deficits in simple word fluency. Although functional neuroimaging studies have provided detailed data regarding prefrontal dysfunction during word fluency tasks, the regions that relate to deficits in fluency of ideas and thoughts have not yet been clarified in schizophrenia patients. The purpose of the present study was to identify the prefrontal sub-regions responsible for deficits in idea fluency using near-infrared spectroscopy (NIRS), which is more practical than other imaging methods, and to investigate the relationships between lesions and idea fluency deficits and social dysfunction in patients with schizophrenia. Eighteen outpatients with schizophrenia and 16 healthy subjects were recruited for this case-controlled study. Using 24-channel NIRS, we measured changes in hemoglobin concentration in the prefrontal cortical surface area during idea and letter fluency tests. The analyses revealed that schizophrenia patients generally exhibited a smaller increase in the concentration of oxyhemoglobin in the frontopolar region than the controls during both the tests. However, the areas in which reduced activations were demonstrated in the patients differed remarkably between the idea and letter fluency tests: reduced activations were observed in the ventral region during the former test and in the dorsal region of the frontopolar cortex during the latter test. The reduced activations in each sub-region appeared to affect the related cognitive impairment, since the patients showed significant poorer performances than the controls on both the tests. Moreover, hypoactivity during idea fluency was significantly correlated with poor social functioning as assessed using the Global Assessment of Functioning (GAF) in the patient group. The results of the present study suggest that the ventral region within the frontopolar cortex is responsible for divergent thinking, which is associated with poor social functioning in patients with schizophrenia.

1. Introduction

The performances on verbal fluency tasks, which are widely used as neuropsychological tests of frontal lobe function, are commonly impaired in patients with schizophrenia (Bokat and Goldberg, 2003; Bowie et al., 2004; Gruzelier et al., 1988; Joyce et al., 1996), and poor verbal fluency is thought to be one of the severest neurocognitive impairments in that population (Harvey and Sharma, 2002). Functional imaging studies, most commonly functional magnetic resonance imaging (fMRI), have revealed prefrontal dysfunction during the letter and category versions of the word fluency test in patients with schizophrenia. In recent years, near-infrared spectroscopy (NIRS) has increasingly and successfully been employed in functional activation studies in schizophrenia subjects because NIRS is a noninvasive and practical imaging method (Ehlis et al., 2007). NIRS measures the concentrations of oxyhemoglobin ([oxy-Hb]) and deoxyhemoglobin ([deoxy-Hb]), which are assumed to reflect the regional cerebral blood volume (rCBV), that is, the activation of a particular brain region (Hoshi and Tamura, 1993).

Meanwhile, a number of studies have cited verbal fluency deficits as important predictors of functional outcome in schizophrenia patients (Green, 1996; Green et al., 2000). In previous studies, we demonstrated the presence of deficits in divergent thinking using the idea fluency test, which is regarded as a more complicated and higher-order form of verbal fluency tests than simple word fluency tests, in patients with schizophrenia (Nemoto et al., 2005; Yamashita et al., 2005). Furthermore, we revealed that deficits in generating high-quality responses requiring a change in viewpoint and flexibility on the idea fluency test were one of the most important determinants of impairments in social functioning in patients with schizophrenia (Nemoto, et al., 2007).

Abbreviations: DLPFC, dorsolateral prefrontal cortex; GAF, Global Assessment of Functioning; ICD-10, International Classification of Diseases, Tenth Revision; IFT, idea fluency test; LFT, letter fluency test; NIRS, near-infrared spectroscopy; PANSS, Positive and Negative Syndrome Scale.

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The recent development of a multi-channel NIRS system has enabled a noninvasive functional mapping of the cerebral cortex. Takizawa et al. (2008) described active sub-regions in the prefrontal cortex during the letter version of the word fluency task in patients with schizophrenia. Although a lesion study revealed that the frontal lobe is involved in the performance of idea fluency as well as word fluency (Saito, 1996), the cortical area responsible for deficits in idea fluency in patients with schizophrenia had remained unclear.

The first aim of the present study was to use NIRS to identify the prefrontal sub-regions responsible for deficits in idea fluency in patients with schizophrenia. The second aim was to investigate the relationship between functional brain activity for idea fluency and social functioning.

2. Methods

2.1. Participants

Eighteen Japanese outpatients with schizophrenia and 16 age- and gender-matched healthy control subjects were recruited for the present study (Table 1). All the participants were right-handed according to the Edinburgh Inventory (Oldfield, 1971). The control subjects were volunteers. Two trained psychiatrists diagnosed the patients using the ICD-10 criteria (World Health Organization, 1993). The mean age of the patients was 25.4 years, and the mean number of years of formal education was 12.8. Their mean duration of illness was 2.7 years, and the mean age at onset was 22.3 years old. The mean score on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) was 28.4 in the patient group. Although all the patients were taking antipsychotic medications, the patients had hardly any extra-pyramidal symptoms.

None of the subjects had a history of alcohol dependence, substance abuse, or serious neurological illness. Clinical interview confirmed that the healthy controls did not have any current and previous psychiatric disorders, and familial history of psychosis. The institutional review board of the Toho University School of Medicine approved the protocol of the present study. The study was performed in accordance with the latest version of the Declaration of Helsinki. After providing the subjects with a complete description of the study, written informed consent was obtained from each subject. On the same day as the NIRS experiment, neurocognitive function, psychiatric symptoms, and social functioning were also evaluated by psychiatrists who were unaware of the NIRS data.

2.2. Measures

2.2.1. Activation task

Changes in the concentration of hemoglobin ([Hb]) were measured during a cognitive activation task. Each participant sat on a chair with their eyes open throughout the measurements. The subjects were instructed to minimize their movements, such as head movements, strong biting and eye blinking, during the NIRS measurements, as such movements can produce artifacts or changes in cerebral perfusion unrelated to the task. The cognitive activation task included a 60-s pre-task baseline, a 300-s idea fluency task (60-s task for the word fluency task), and a 60-s post-task baseline.

We used the idea and letter fluency tests (Nemoto et al., 2005) as activation tasks. In the idea fluency test (IFT), the examiner asked the subject to think of as many uses for an empty tin can as possible within 5 min. The responses generated were classified into three groups: task-dependent responses that were defined as common and stereotyped ideas, task-modified responses that required a change in viewpoint and flexibility, and task-independent responses that were derived from fresh conceptions arising above the characteristics of the stimulus. The task-modified and task-independent responses were considered as creative and active responses and were regarded as "high-quality" responses. The total number of each kind of response generated was used as the score. For the pre- and post-task periods of the IFT, the subjects were asked to keep their eyes open and to remain silent in consideration of the productivity of responses in the IFT. In the letter fluency test (LFT), the examiner asked the subjects to generate as many words as they could, using three syllables (/shi/, /i/, and /re/, each for 20 s) continuously. This task is often used for cognitive activation in NIRS studies. For the pre- and post-task periods of the LFT, the subjects were instructed to repeat the vowel sounds (/a/, /i/, /u/, /e/, /o/) continuously.

2.2.2. NIRS measurement

The 24-multi-channel NIRS machine (OMM3000, Shimadzu Co., Japan) used in this study measures the relative changes in [oxy-Hb] and [deoxy-Hb] using two wavelengths (695 nm and 830 nm) of infrared light, based on the modified Beer–Lambert law (Yamashita et al., 1996). The [total-Hb] was calculated as the sum of [oxy-Hb] and [deoxy-Hb]. These [Hb] values include a differential pathlength factor (DPF). The distance between pairs of source-detector probes was set at 3.0 cm, and we defined each measuring area between pairs of source-detector probes as a channel. When the source-detector spacing is set at 3.0 cm, the machine is thought to measure changes at points 2–3 cm below the scalp, that is, on the surface of the cerebral cortex (Okada and Delpy, 2003a,b). The probes of the NIRS machine were fixed with thermoplastic 4×6 shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The 24 measuring areas were labeled ch 1–24 from the right posterior to the left anterior. This arrangement of the probes covering an area surrounded with the Fp1, Fp2, F3, and F4 positions in the 10–20 system approximately can be used to measure [Hb] in bilateral prefrontal cortical surface regions that correspond to Brodmann's areas (BA) 9 and 10 (Okamoto et al., 2004).

The time resolution of the NIRS machine was set at 0.1 s. [Hb] changes were analyzed using a first-order correction to exclude task-unrelated changes during cognitive activation tasks. The pre-test baseline was determined as the mean across the 60 s of the pre-task period. Grand mean waveforms averaged across subjects were created separately according to the type of [Hb] and for each group.

2.2.3. Symptoms and social functioning

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to obtain scores on the positive symptoms subscale, negative symptoms subscale, and general psychopathology subscale. The Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) was used as the scale to measure global social functioning.

2.3. Statistical analysis

For the data analysis using parametric statistical tests, the [Hb] data obtained from each channel were averaged across the two time

Table 1
Demographic and clinical characteristics of the schizophrenia group and the control group.

	Schizophrenia (n = 18)		Controls (n = 16)	
	Mean	SD	Mean	SD
Gender (M/F)	7/11		8/8	
Age (year)	25.4	5.8	24.5	3.4
Education (year)	12.8	2.5	15.7	1.9
MMSE	28.4	1.8		
Age at onset (year)	22.3	5.4		
Duration of illness (year)	2.7	2.4		
Medication (CPZ eqv.)	485.9	321.5		
PANSS				
Positive	22.8	3.7		
Negative	27.0	4.0		
General	53.8	6.0		
GAF	64.7	6.6		

CPZ: chlorpromazine, GAF: Global Assessment of Functioning, MMSE: Mini-Mental State Examination, PANSS: Positive and Negative Syndrome Scale.