2. Methods

2.1. Subjects

Subjects were 86 patients with chronic schizophrenia who were under treatment at the National Center of Neurology and Psychiatry Musashi Hospital, Tokyo, Japan. All met the DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia. Consensus diagnoses were made based on clinical interviews, observations and case notes by clinicians who were all senior psychiatrists. One hundred and fifteen age- and gender-matched healthy volunteers were recruited from hospital staff and their associates through flyers and by word of mouth, and also from the community through local newspaper advertisements, our website announcement, and notices posted on bulletin boards at a college. Healthy participants were interviewed for enrollment using the Japanese version of the Mini-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998; Otsubo et al., 2005) by a research psychiatrist (H.H.), and only those who demonstrated no history of psychiatric illness or contact to psychiatric services were enrolled as healthy controls. Participants were excluded from both the patient and control groups if they had a prior medical history of central nervous system disease or severe head injury, or if they met DSM-IV criteria for mental retardation, substance dependence, or substance abuse within the past 6 months. All subjects were biologically unrelated Japanese who resided in the Western part of Metropolitan Tokyo.

Written informed consent was obtained from all subjects prior to their inclusion in the study and the study was approved by the ethics committee of the National Center of Neurology and Psychiatry (NCNP), Japan.

2.2. Personality assessment

Personality was assessed in all subjects with the Temperament and Character Inventory (TCI, Cloninger et al., 1993). TCI is a 240-item (including 14 items which are not analyzed) self-report questionnaire; each item requires a true/false answer. The term *temperament* refers to automatic emotional reactions to subjective experiences that may be genetically transmitted and therefore stable over time. Four dimensions of temperament are distinguished by the TCI: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS). NS, HA, and RD have been assumed to relate to dopaminergic, serotonergic, and noradrenergic neurotransmission, respectively (Cloninger, 1987). This model, therefore, may be particularly relevant in schizophrenia since such neurotransmitters are involved in symptom expression and are the main targets of antipsychotic medication (Markianos et al., 2001). The term *character* refers to concepts pertaining to the individual, focusing on personal differences in intentions, decisions and values. Three dimensions of character are distinguished: self-directedness (SD), cooperativeness (CO), and self-transcendence (ST). The reliability and validity of the original American version of the TCI in general community dwellers and in

psychiatric patients have been established (Cloninger et al., 1993; Svrakic et al., 1993). Moreover, the TCI has been translated into and validated in more than 7 languages including Japanese (Kijima et al., 1996, 2000), and used in many genetic (Benjamin et al., 1996; Ebstein et al., 1996) and clinical studies (Eklund et al., 2004; Cloninger et al., 2006). The Japanese version of the TCI translated by Kijima et al. (1996) was used in the present study. The questionnaire was distributed to both patients and controls at the hospital and at our laboratory, respectively. Each subject was allowed to take as much time as needed to complete the questionnaire, then returned it to us by mail or by hand.

2.3. Clinical assessment and antipsychotic medication

Schizophrenic symptoms were assessed by an experienced research psychiatrist (H.K.) in 53 (male, 31; female, 22) of 86 patients using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987); this yields a total score in addition to scores on positive, negative, and general psychopathology subscales. All patients with schizophrenia were receiving antipsychotic agents and were clinically stable at the time of the personality evaluation. Daily doses of antipsychotics, including depot antipsychotics, were converted to chlorpromazine equivalents (CPZeq) using published guidelines (American Psychiatric Association, 1997; Inagaki et al., 1999).

2.4. Statistical analyses

Demographic characteristics and TCI scores were compared between groups. Means and categorical variables were compared using the analysis of variance (ANOVA) and the χ^2 test, respectively. Pearson's r was used to examine correlations. One-way ANOVA with Bonferroni correction, allowing for multiple comparisons, was performed to examine differences between 3 groups. The analysis of covariance (ANCOVA) was used to compare TCI scores between groups, controlling for confounding variables. Statistical significance was set at two-tailed $P < 0.05$. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Japan, Tokyo).

3. Results

3.1. Sample characteristics

Tables 1 shows the characteristics of patients with schizophrenia and healthy controls (both are stratified by gender), respectively. Patients with schizophrenia and healthy controls did not differ in age ($F(1,199) = 0.033$, $P = 0.86$) or gender ($\chi^2(1) = 0.00026$, $P = 0.99$), but patients demonstrated significantly fewer years of education as compared with controls ($F(1,199) = 51.1$, $P < 0.001$). Schizophrenic males and females did not significantly differ in any of the characteristics examined. Control males and females did not differ in age, but control males had received significantly more years of education than females. Education was significantly correlated with RD ($r = -0.22$, $P = 0.02$) and PS ($r = 0.35$, $P < 0.001$) in healthy controls, thus in ANCOVA it was used as a covariate where appropriate.

3.2. TCI scores of patients vs. controls

TCI scores of patients with schizophrenia and control subjects are presented in Table 2. All personality dimensions except PS, namely 6 dimensions, were significantly different between patients and controls using ANOVA; patients showed significantly higher scores on HA and ST and lower scores on NS, RD, SD and CO than controls.

These differences between patients and controls in the 6 dimensions all remained significant after ANCOVA was performed with education years as a covariate.

3.3. Gender differences in TCI scores

3.3.1. TCI scores of male patients vs. female patients

When TCI scores were compared between male and female patients using ANOVA, male patients showed significantly higher HA ($F(1,84) = 5.23$, $P = 0.025$) than female patients. In addition, male patients demonstrated lower SD ($F(1,84) = 3.78$, $P = 0.055$) and CO ($F(1,84) = 3.46$, $P = 0.066$) than female patients with statistical trend.

3.3.2. TCI scores of male patients vs. female patients vs. controls (male & female combined)

Fig. 1 shows comparisons of 3 groups (male patients/female patients/total controls) using one-way ANOVA with Bonferroni correction. Regarding RD and CO, male patients, but not female patients, significantly differed from controls. Concerning NS, HA, SD and ST, both male and female patients significantly differed from controls. In this analysis, male and female patients did not significantly differ in any of the 7 personality dimensions.

3.4. Correlations between TCI scores and clinical variables (including symptoms) of

patients

Duration of illness showed a significantly negative correlation with NS (r = -0.23, P = 0.036). CPZeq showed a significantly positive correlation with PS (r = 0.23, P = 0.04) and ST (r = 0.22, P = 0.04). Correlations between scores of TCI and PANSS are presented in Table 3. Family history of psychiatric disease, age at onset, and number of hospitalizations were not correlated with any of the TCI dimensions.

3.5. Comparisons of TCI scores in patients and controls between prior studies and ours

Table 4 shows a comparison of our TCI results and those of the two previous studies (Guillem et al., 2002; Boeker et al., 2006) which examined the personality of patients with schizophrenia using TCI with a cross-sectional case-control design. All directions of differences between patients and controls in TCI dimensions, except for RD, were consistent in these three studies. Lower SD in patients with schizophrenia was the most consistent finding. Lower NS and CO and higher HA and ST in patients were quite consistent. Lower PS in patients was also consistent, but not of great statistical significance. In addition, Calvo de Padilla et al. (2006) reported with an indigenous sample of Argentina that patients with schizophrenia showed significantly lower RD, SD and CO compared to community controls (their data are not integrated into Table 4 because mean scores of TCI were not presented in their paper).

4. Discussion

In this study we report personality, as assessed with the TCI, in patients with schizophrenia compared to healthy subjects. Patients with schizophrenia demonstrated marked alteration of personality. Male patients seemingly showed greater alteration than female patients.

4.1. Personality traits in patients with schizophrenia

Our results indicate that patients with schizophrenia have pervasively altered personalities. Furthermore, the findings of the present and prior two studies (Guillem et al., 2002; Boeker et al., 2006), as shown in Table 4, are fairly consistent with each other. Guillem et al. (2002) reported that patients with schizophrenia showed significantly higher HA, and lower NS, PS, SD and CO compared to healthy controls, all of which were congruent with the present study, although the lower PS in our patients just failed to reach statistical significance. In contrast, RD and ST showed significant differences between the two diagnostic groups only in the present study. These could mainly be attributed to the larger sample size in the present study since the patterns of differences in mean scores on RD and ST between patients and controls were similar in these two studies. Moreover, Boeker et al. (2006) found that patients with schizophrenia showed significantly lower SD and CO and higher ST than healthy subjects, all of which

corroborated our results. In addition, Calvo de Padilla et al. (2006) reported that patients with schizophrenia showed significantly lower RD, SD and CO compared to controls, all of which were also in line with our results. In general, our findings confirmed and extended the prior ones in that patients with schizophrenia have unique personality profile, in which lower SD is the most prominent abnormality. These findings may be of clinical importance, taking account of the studies that reported TCI scores, especially SD, were related to level of functioning and psychological health (Eklund et al., 2004) and to subjective quality of life (Hansson et al., 2001) in patients with schizophrenia.

On the other hand, cross-cultural differences in personality assessed with the TCI may exist (Pélissolo and Lépine, 2000; Brändström et al., 2001). Indeed, mean scores for both patients and controls on each dimension of TCI were substantially different between our subjects and the prior ones. Further, these differences of TCI scores between studies within the same diagnostic groups were of comparable size to the differences between patients and controls within each study.

The most plausible explanation may be that although personality itself may vary across cultures, it may be a worldwide phenomenon that patients with schizophrenia collectively have markedly different personality profiles from healthy people in their own cultural group, especially regarding NS, HA, SD, CO and ST.

Moreover, the fact that the NEO-FFI higher neuroticism and lower extraversion and conscientiousness in schizophrenia patients are well-established findings (Gurrera et al., 2000; Pillmann et al., 2003; Camisa et al., 2005), coupled with the substantial overlap

between NEO-FFI and TCI dimensions (e.g., positive correlation between neuroticism and HA, negative correlation between neuroticism and SD, and positive correlation between conscientiousness and PS) (De Fruyt et al., 2000; MacDonald and Holland, 2002; Ramanaiah et al., 2002), would theoretically predict the following TCI results in schizophrenia patients: high HA, low PS, low SD. Indeed, these predictions are largely in accord with our actual results as well as with previous TCI findings. Regarding NS, positive correlation with extraversion and negative correlation with conscientiousness have simultaneously been reported (De Fruyt et al., 2000; MacDonald and Holland, 2002; Ramanaiah et al., 2002); however, since both extraversion and conscientiousness are low in schizophrenia, it is impossible to examine the compatibility of this TCI dimension with the NEO findings. In short, the personality profile of schizophrenia patients as assessed by the TCI showed a compatible pattern with that assessed by NEO-FFI. All in all, the hypothesis (i) has largely been supported.

4.2. Gender differences in personality among schizophrenia patients

The hypothesis (ii) was partly supported in that male patients showed even greater personality alteration than female patients (when both groups are compared to controls) for the two dimensions, RD and CO (Fig. 1). These results are in harmony with a precedent study that reported schizophrenic males showed greater abnormality in premorbid personality than schizophrenic females (Foerster et al., 1991). Gender

differences have already been reported concerning other important variables in schizophrenia such as age at illness onset, premorbid functioning, symptomatological characteristics, and neuropsychological function (Castle et al., 1993; Leung and Chue, 2000). Generally, male patients with schizophrenia tend to be more severely ill than their female counterparts as shown by earlier age of onset, poorer premorbid functioning, severer cognitive deficits, and higher risk of having a deficit state (Castle et al., 1993; Leung and Chue, 2000). Some of these gender differences might reflect the gender difference in personality in the present study, in which male patients apparently showed more unique personality profiles than female patients.

4.3. Relationships between personality and symptom dimensions

In the present study, since TCI dimensions were somewhat correlated with schizophrenic symptoms and dosage of antipsychotics, personality might be affected by illness severity. For instance, ST was positively correlated with positive symptoms and dosage of antipsychotics, suggesting that this personality dimension could be substantially related to the severity of positive symptoms. This positive correlation between ST and psychotic symptoms has also been found in the precedent study (Guillem et al., 2002) which used the three-dimensional model of Andreasen et al. (1995) and the five-dimension model of Toomey et al. (1997) for assessment of symptoms. In addition, Guillem et al. (2002) have reported that psychotic symptoms are

positively correlated with NS and negatively with SD, both of which were not replicated in the present study. Instead, in the present study negative symptoms were negatively correlated with RD, PS and CO. These correlations in the present study appear to be plausible, given that the negative subscale of PANSS is composed of items which assess, for example, "blunted affect", "passive social withdrawal", and "poor rapport". These relationships observed between personality and symptom dimensions were in support of our hypothesis (iii). The inconsistencies between studies might be due in part to the differential instruments of symptom assessment used, and require further investigations.

4.4. Strengths and limitations of the study

A major advantage in this study was that we examined personality by using the TCI, which has a number of merits in personality research that have already been mentioned in the present report. Sample size of the present study was the largest of the four personality studies of schizophrenia where the TCI was used (Guillem et al. 2002; Boeker et al. 2006; Calvo de Padilla et al. 2006). Moreover, our patients and controls were matched for age and gender, and male and female patients were similar to each other regarding all clinical variables examined, both of which made further comparisons by gender relatively free from confounders. On the other hand, education was significantly different between patients and controls or control males and females, but the lowered education in schizophrenia could be closely related to the illness itself. It

should also be noted that in Japan it is common for men to achieve higher educational status than women. Thus our subjects, both patients and controls, are likely to be representative of the general Japanese population in terms of education.

There are several limitations to this study. First, its cross-sectional nature does not permit any definite conclusions as to whether personality traits we found to be altered in schizophrenia are premorbid ones or the results of changes after illness onset. Second, personality assessment was based on self-report, thus not objective. However, our results that showed moderate correlations between TCI and PANSS scores might suggest that the results of subjective personality assessment with the questionnaire were corroborated by those of objective symptom assessment. Third, since our sampling was not community-based random sampling, it is possible that certain sampling biases existed; people who had high "novelty seeking", for example, were likely to become interested in this study. Finally, our patients with schizophrenia were chronic, which precluded extrapolation of the results to recent-onset patients.

4.4. Conclusions

The present findings indicate that patients with chronic schizophrenia have pervasively altered personality profile as measured by TCI which is in line with previous studies, and male patients may undergo even more pronounced personality alteration than female patients when both of them are compared to healthy people.

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