1. Introduction

Diffusion tensor imaging (DTI) (Basser et al., 1994), a newly developed method to estimate the white matter (WM) integrity, provides information about the diffusion of water in biological tissues. In the WM, water diffusion is highly anisotropic, with greater diffusion in the direction parallel to axonal tracts. Thus, diminished anisotropy of water diffusion has been proposed to reflect compromised WM integrity (Lim et al., 1999). Fractional anisotropy (FA) (Basser, 1995) is a quantitative measure of diffusion anisotropy acquired from DTI.

The normally aging brain exhibits an assortment of micro- and macroscopic changes in the WM as well as the cerebral cortex. Histological studies demonstrate a decrease in myelin density and in the number of myelinated fibers (Meier-Ruge et al., 1992). Postmortem brain (Meier-Ruge et al., 1992) and volumetric neuroimaging studies (Christiansen et al., 1994; Salat et al., 1999) have suggested that WM changes are more prominent than cortical changes with aging, at least during certain segments of the age span and in certain regions of the brain. For example, volume loss in prefrontal WM is disproportionately greater than that in prefrontal cortex with late aging {comparison of elderly adults aged 60–75 with those aged >85 years (Salat et al., 1999)}. Several DTI studies have demonstrated age-related reductions of WM anisotropy in the genu of the corpus callosum (Pfefferbaum et al., 2000b), anterior WM (Pfefferbaum et al., 2000a; O'Sullivan et al., 2001), periventricular WM (Nusbaum et al., 2001), and the prefrontal WM (Nusbaum et al., 2001; Pfefferbaum et al., 2005; Salat et al., 2005).

Regarding schizophrenia, impairments of the neural connectivity between certain cortical areas, such as frontal and temporal areas, have been implicated in the pathophysiology of the disease (Frith and Dolan, 1996; Andreasen et al., 1997; Bullmore et al., 1997). Indeed, volumetric magnetic resonance (MR) studies and pathological studies demonstrated abnormalities of the WM in schizophrenia (Miyakawa et al., 1972; Cannon et al., 1998; Davis et al., 2003; Ho et al., 2003; Uranova et al., 2004). Changes in WM integrity in schizophrenia has relevance to the neural disconnection model of the disorder and may provide a basis for focal abnormalities as well. Several previous DTI studies in chronic schizophrenia showed decrease of FA in schizophrenics mainly in the front-temporal white matter and corpus callosum (Buchsbaum et al., 1998; Lim et al., 1999; Agartz et al., 2001; Burns et al., 2003). Furthermore, FA decrease in patients with first episode schizophrenia might be less pronounced compared to chronic patients (Price et al., 2005; Szeszko et al., 2005), suggesting that the decreased FA in schizophrenics might be attributed, at least in part, to progressive and exaggerated age-dependent changes in schizophrenics rather than neurodevelopmental abnormalities in the WM. To date, there is only one cross-sectional study with a small sample size investigating age-related FA changes in schizophrenia that demonstrated an age-related FA increase in schizophrenics (Jones et al., 2006).

The present study was aimed to examine whether patients with chronic schizophrenia do have reduced FA values compared to controls and whether such changes in FA progress in an age-dependent manner.

2. Methods

2.1. Subjects

Table 1 shows the characteristics of participants of this study. Forty-two patients with chronic schizophrenia were recruited at the National Center of Neurology and Psychiatry, Tokyo, Japan. Consensus diagnosis was made for each patient by at least two trained psychiatrists according to the DSM-IV criteria (American Psychiatric Association, 1994), based on all available information, including clinical interviews, medical records and other research assessments. All patients were stable and/or partially remitted and had been taking antipsychotic medication at the time of MR measurement and neuropsychological tests. Forty-two healthy volunteers who had no current or past contact to any psychiatric services served as controls. All the subjects were biologically unrelated Japanese. After description of the study, written informed consent was obtained from every subject. The study protocol was approved by the ethics committee of the National Center of Neurology and Psychiatry, Tokyo, Japan. Exclusion criteria for all the participants included asymptomatic or symptomatic cerebral infarctions detected by T2 weighted MRI, serious neurological or endocrine disorder, any medical condition that could potentially affect the central nervous system, or mental retardation according to DSM-IV criteria.

2.2. Image acquisition

MR studies were performed on a 1.5 tesla Magnetom Vision Plus system (Siemens, Erlangen, Germany). Axial DTI scans aligned to the plane containing anterior and posterior commissures were acquired with a pulsed-

Table 1
Characteristics of participants

	Controls	Schizophrenics	Two sample *t*-test	(Two-tailed; df=82)
			t	*P*
Number of subjects	42	42		
Gender (male/female)	26/16	26/16		
Handedness (right/left)	41/1	41/1		
Age (years)	39.2 (9.0)	40.0 (9.3)	−0.42	0.68
Range of age (years)	22–59	22–59		
Education (years)	17.1 (3.5)	13.0 (2.9)	8.1	<0.001
Full-scale IQ (WAIS-R)	114.3 (11.6)	86.0 (21.3)	6.0	<0.001
Age of onset		23.3 (7.0)		
Duration of illness (years)		16.8 (9.0)		
Duration of hospitalization (months)		31.2 (61.3)		
Dose of total antipsychotic drugs (mg/day, chlorpromazine equivalent)		1005.1 (735.3)		
Dose of typical antipsychotic drugs (mg/day, chlorpromazine equivalent)		694.8 (748.3)		
Dose of atypical antipsychotic drugs (mg/day, chlorpromazine equivalent)		310.3 (464.2)		

Mean (S.D.).
WAIS-R: Wechsler Adult Intelligence Scale-Revised.

gradient, spin-echo, single-shot echo planar imaging (EPI) sequence (TR/TE=4000/100 ms; acquisition matrix, 256×256; NEX=4, FOV 240 mm; b=1000 s/mm^2; 20 slices, slice thickness 5 mm, gap 1.5 mm). Diffusion was measured along six non-collinear directions. For each of six gradient directions, four acquisitions were averaged. Four acquisitions without diffusion weighting (b=0) were also averaged. Additionally, a three dimensional volumetric acquisition of a T1-weighted gradient echo sequence with a gapless series of thin sagittal sections using an MPRage sequence (TR/TE=11.4/4.4 ms; flip angle, 15 degree; acquisition matrix, 256×256; NEX=1, FOV 315 mm; slice thickness 1.23 mm) was acquired for evaluating the volume of grey matter (GM), WM and cerebrospinal fluid (CSF) space.

2.3. Image processing

FA images for each subject were computed from seven diffusion images acquired as above by an in-house script on Matlab 6.5 software (Mathworks, Inc., MA, USA). Then, the FA images were spatially-normalized using high-dimensional-warping algorithm (Ashburner et al., 1999) and were matched to the FA template image. To make the FA template image, we warped FA images of 4 normal subjects (other than 42 control subjects) to the single-subject T1 template (skull stripped image) using spatial normalization function of SPM2 and averaged the 4 warped FA images. The transformed FA images were smoothed with a Gaussian kernel. The filter size (full-width at half-maximum: FWHM) was varied from zero to 16 mm in steps of 2 mm to validate the consistency of results of SPM analyses, because a previous study (Jones et al., 2005) reported that the statistical results of SPM analyses were differed depending on filter size. For measuring the volume of GM, WM and CSF space, an additional function of an optimized VBM script (http://dbm.neuro.uni-jena.de/vbm) was used (Good et al., 2001).

2.4. Statistical analysis

2.4.1. Voxel-by-voxel analysis

The resultant FA images were analyzed using statistical parametric mapping with the framework of the General Linear Model in SPM2 (Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). We constituted following three

Table 2
The relationship between smoothing kernel sizes (FWHM) and number of resels in our sample

FWHM (mm)	Number of resels
None	12460.4
2×2×2	5131.1
4×4×4	1720.2
6×6×6	706.0
8×8×8	289.4
10×10×10	119.7
12×12×12	52.1
14×14×14	24.4
16×16×16	12.4

statistical analyses: 1) a two-sample *t*-test for estimating group differences (controls versus schizophrenics), 2) a correlational analysis between age and FA values in both controls and the schizophrenics and 3) a correlational analysis of FA values with duration of illness, age of onset, duration of hospitalization, and daily dose of

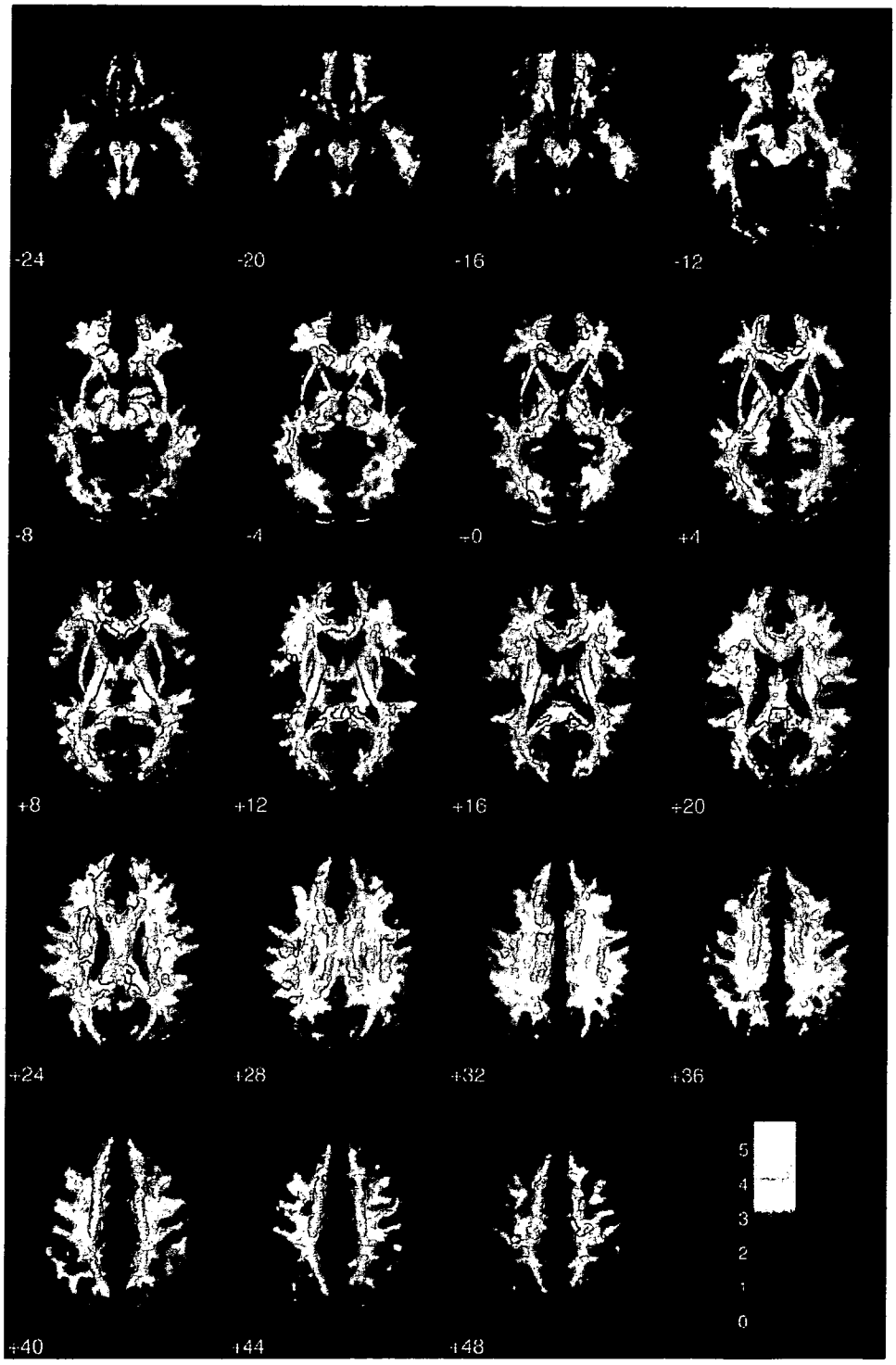

Fig. 1. Comparison in FA values between patients with schizophrenia and controls. The SPM {t} is displayed onto axial FA template images. The WM areas in which significantly lower FA values in patients compared with controls were observed, including the bilateral frontal and temporal WM, uncinate fasciculi, cingulum bundles, and genu and splenium of the corpus callosum ($P<0.001$, uncorrected).

antipsychotic drugs in the schizophrenics. In all the three analyses, relative WM volume (WM volume divided by the summation of GM, WM and CSF volumes) and WAIS-R (Wechsler Adult Intelligence Scale-Revised) full-scale IQ score were treated as nuisance variables. The former was included for eliminating the possible effect of WM volume change associated with aging on the FA values through partial voluming from non-WM voxels. The latter was included to allow for the effects of IQ, because there was some evidence which suggested DTI measures were correlated with cognitive decline in elderly (O'Sullivan et al., 2004). We additionally conducted the analyses without these two nuisance variables to check whether there were any differences in the results with or without nuisance variables in the statistical models. To estimate population effects (diagnostic effects), we used a single-subject, condition (controls or schizophrenics) and covariate (no covariate of interest) model for the SPM analysis. In the second analysis, we applied the single subject condition (controls or schizophrenics) and covariate (interaction with condition, covariate of interest; age) model. A single-subject, covariate only model was applied in the third analysis. For these three analyses, we set masking threshold for FA values of 0.2 for excluding voxels containing partial volume of WM and other tissues. Since the previous study demonstrating a positive correlation between FA values and age in schizophrenics reported mean FA values of around 0.4 (Jones et al., 2006), we additionally set masking threshold for FA values of 0.35 for examining correlation between age and FA values of more anisotropic WM structure in the second analysis. For the evaluation of the statistical models, we used Wake Forest University Pickatlas (Maldjian et al., 2003) to pick up cerebral WM in the Montreal Neurological Institute (MNI) space. We used uncorrected $P<0.001$ as a statistical threshold to search significant differences. As demonstrated in Table 2, the number of resels differed profoundly depending on smoothing kernel sizes (FWHM) and the statistical results with correction for multiple comparisons could change dramatically relying on number of resels. On the other hand, SPM results without correction for multiple comparisons were essentially unchanged regardless of smoothing kernel size (data not shown). Therefore, we did not perform correction for multiple comparisons. The resultant set of t values constituted statistical parametric map (SPM {t}). We employed the filter size of 6 mm for presentation of the results considering for the original voxel dimensions of acquired data {0.94 mm × 0.94 mm × (5.00+1.50) mm}.

2.4.2. ROI analysis

To ensure the robustness of the results of the voxel-by-voxel analyses, we additionally performed ROI analyses. We used MarsBar (http://marsbar.sourceforge.net/) for extracting region of interest (ROI) containing all the voxels classified as WM with Wake Forest University Pickatlas from spatially normalized and smoothed FA images and calculated mean FA values of the ROI. Then, we performed correlational analyses of mean FA values with the same variables in voxel-by-voxel analysis using Statistical Package for Social Science (SPSS), 1) in both controls and schizophrenics, 2) in controls and 3) in schizophrenics. We constituted a General Linear Model for the first analysis and entered diagnosis-by-age interaction effects into the statistical model to examine if there were any diagnosis-by-age interaction effects. For the second and third analyses, Pearson's correlation coefficients between mean WM FA values and covariates were calculated.

3. Results

3.1. Voxel-by-voxel analyses

3.1.1. Comparison between schizophrenics and controls

Schizophrenics demonstrated significantly lower FA values in widespread WM areas, compared with controls. These WM areas included bilateral frontal and temporal lobes, uncinate fasciculi (external capsules), cingulum bundles, and genu and splenium of corpus

Table 3
The summary of the WM areas in which significantly lower FA values in patients compared with controls were observed

Anatomical regions	t-value	MNI coordinates		
	(Voxel level)	x	y	z
Rt frontal lobe white matter	4.34	22.5	52.5	−4.5
Lt frontal lobe white matter	5.43	−13.5	49.5	−6
Rt temporal lobe white matter	4.25	48	−33	−7.5
Lt temporal lobe white matter	4.19	−45	−31.5	−10.5
Rt uncinate fasciculus (external capsule)	4.00	33	12	−1.5
Lt uncinate fasciculus (external capsule)	3.84	−33	12	−1.5
Rt cingulate bundle	4.23	6	6	33
Lt cingulate bundle	4.32	−7.5	6	30
genu of corpus callosum	3.79	6	24	10.5
splenium of corpus callosum	4.18	−3	−33	19.5

callosum (Fig. 1, Table 3). There would be increased possibility of alpha errors because we did not perform correction for multiple comparisons. However, our results were in well concordance with the results of the previous studies (Buchsbaum et al., 1998; Lim et al., 1999; Agartz et al., 2001; Burns et al., 2003; Kubicki

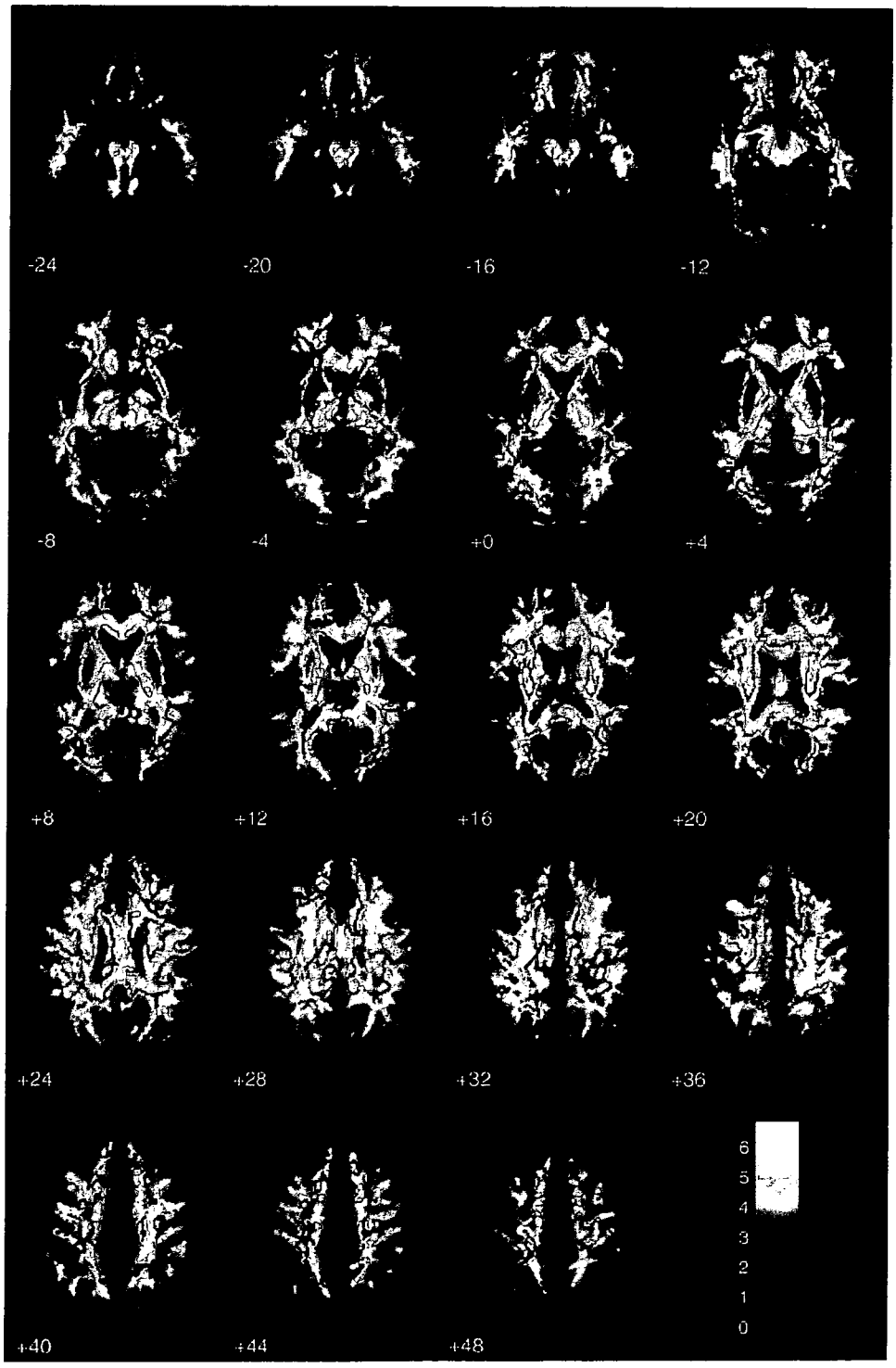

Fig. 2. Correlational analysis between FA values and age with 0.2 as a masking threshold in schizophrenics. The SPM {t} is displayed onto axial FA template images. The widespread WM areas showed a significant negative correlation between FA values and age in schizophrenics ($P<0.001$, uncorrected).

et al., 2003). Therefore, we might be able to regard the results of these previous studies as a priori hypotheses. There were no areas of significantly higher FA values in patients compared with controls even at a lenient threshold ($P<0.05$, uncorrected). In these results of the analysis without nuisance variables in the statistical

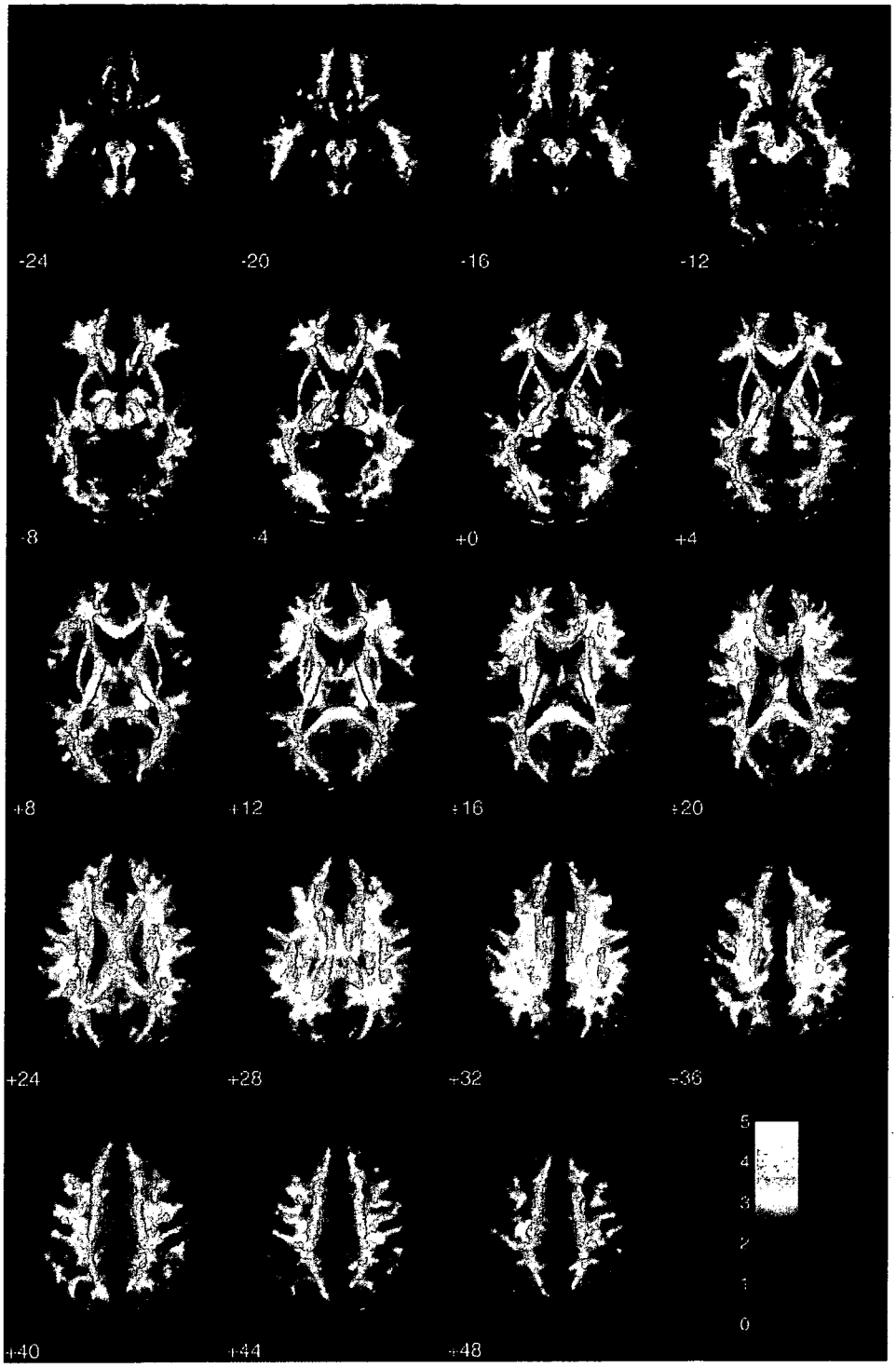

Fig. 3. Correlational analysis between FA values and age with 0.2 as a masking threshold in controls. The SPM {t} is displayed onto axial FA template images. The WM areas showed a significant negative correlation between FA values and age in controls ($P<0.001$, uncorrected), including right prefrontal {(15.0, 49.5, 30.0) in MNI coordinates, $t=5.03$}, left frontal {(−37.5, −15.0, 34.5), $t=4.51$} and bilateral temporo-occipital WM {(31.5, −60.0, 16.5), $t=4.75$; (−30.0, −60.0, 15.0), $t=4.47$}.

models, the distributions of the statistically significant areas were essentially unchanged compared to the results with nuisance variables although the spatial extents of the statistically significant areas were slightly larger (data not shown), which was the case with the results of other two analyses.

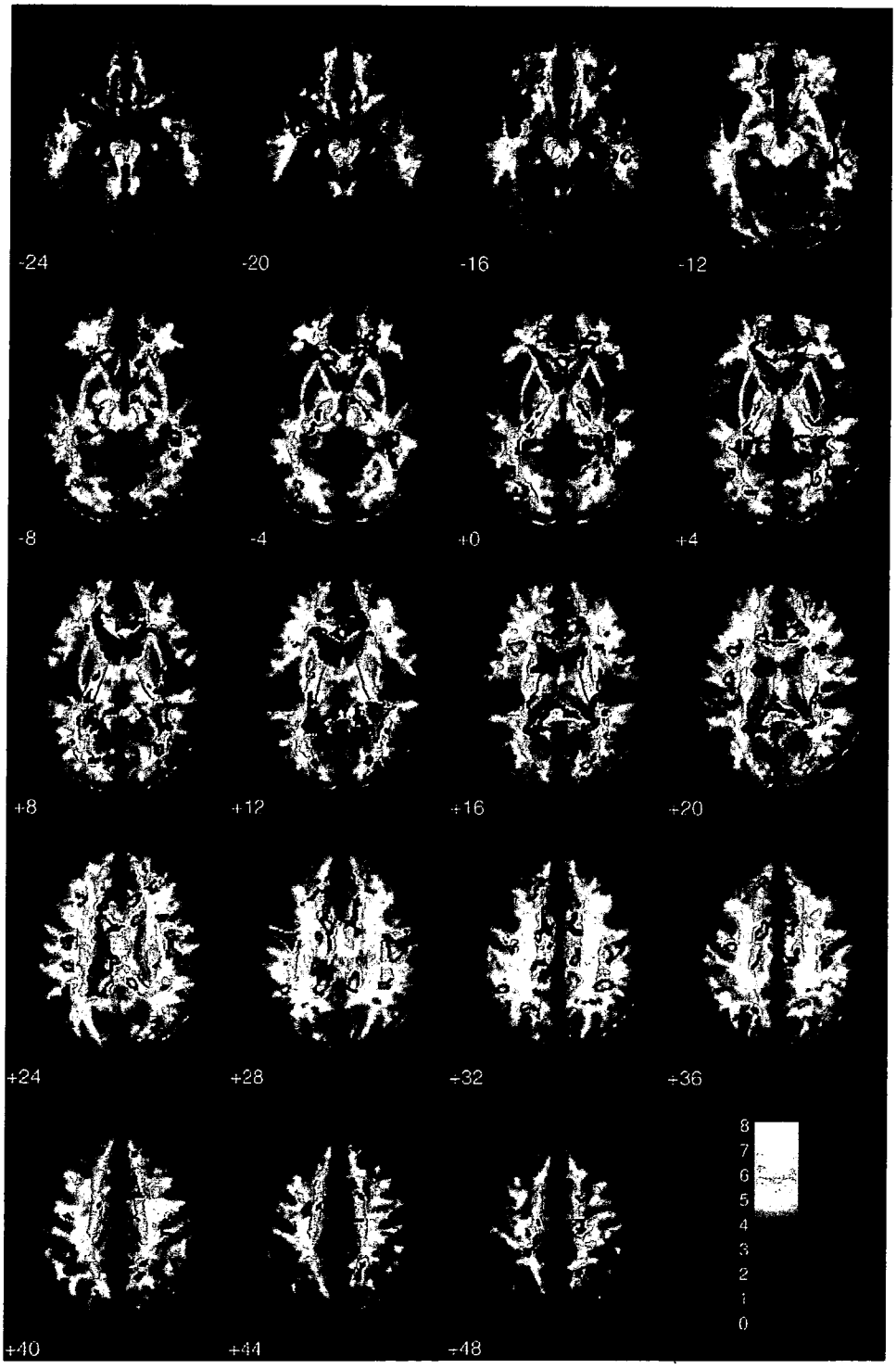

Fig. 4. Correlational analysis between FA values and duration of illness with 0.2 as a masking threshold in schizophrenics. The SPM {t} is displayed onto axial FA template images. The widespread WM areas showed a significant negative correlation between FA values and duration of illness in schizophrenics ($P<0.001$, uncorrected).

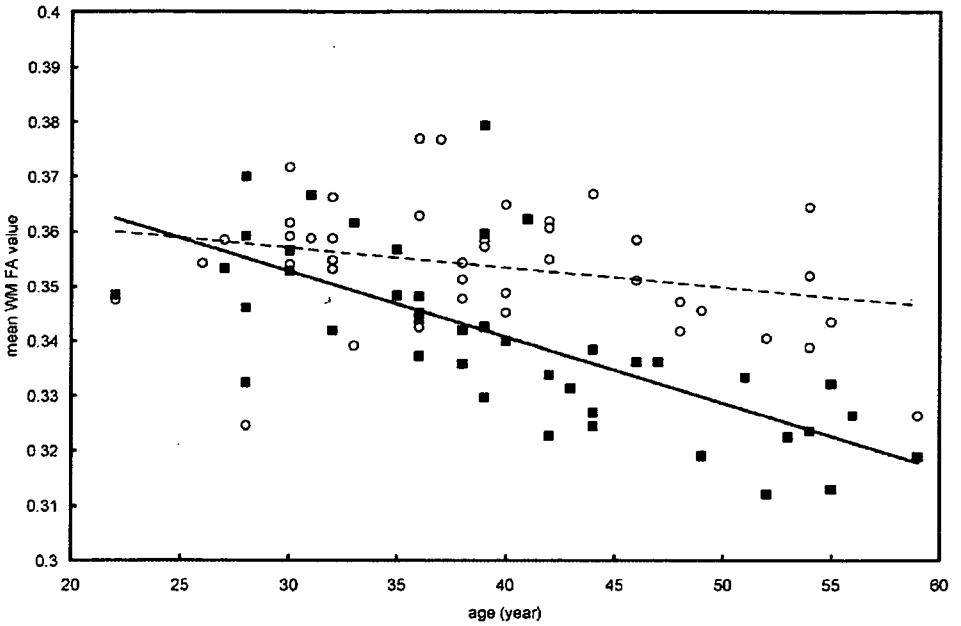

Fig. 5. A scatter plot between age and mean WM FA value when masking threshold for FA values was set to 0.2. Filled squares represent schizophrenics and open circles represent controls. The solid line indicates a regression line for schizophrenics ($y=-0.0012\times+0.3888$, $R^2=0.49$, test for regression slope: df=40; $t=-6.24$; $P<0.0001$). The dashed line indicates a regression line for controls ($y=-0.0004\times+0.3679$, $R^2=0.083$, test f or regression slope: df=40; $t=-1.90$; $P=0.065$). A significant diagnosis-by-age interaction effect (general linear model: $P=0.009$) was noted.

3.1.2. *Correlational analysis in schizophrenic and control groups*

As the results of the second analysis considering aging effects, a significant negative correlation with age was observed in the FA values of widespread, almost diffuse WM areas in the schizophrenic group (Fig. 2), while in the control group, only FA values in right prefrontal {(15.0, 49.5, 30.0) in MNI coordinates, $t=5.03$}, left frontal {(−37.5, −15.0, 34.5), $t=4.51$} and bilateral temporo-occipital WM {(31.5, −60.0, 16.5), $t=4.75$;

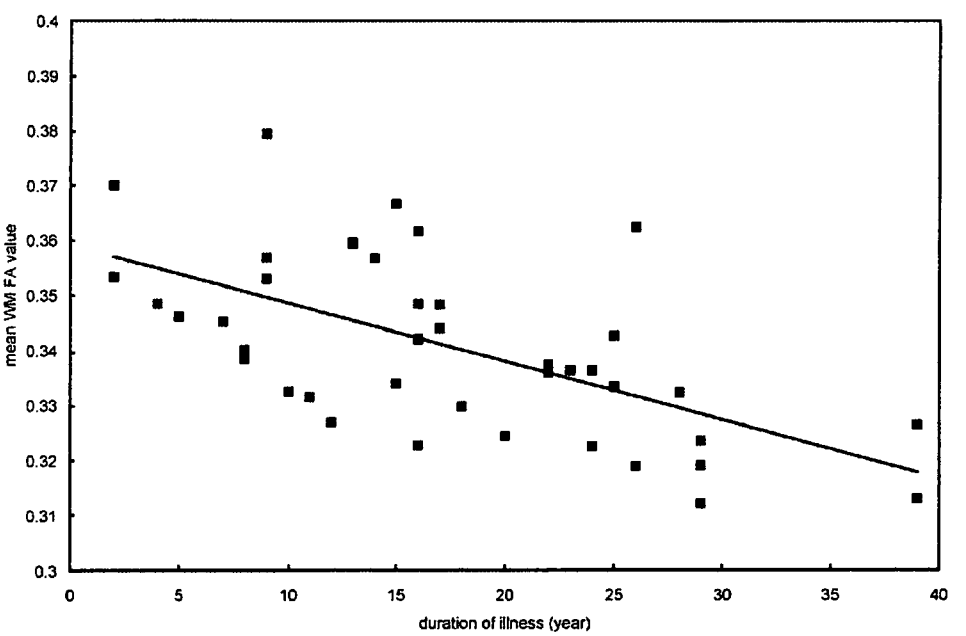

Fig. 6. A scatter plot between duration of illness and mean WM FA value when masking threshold for FA values was set to 0.2. Filled squares represent schizophrenics. The solid line indicates a regression line for schizophrenics ($y=-0.0011\times+0.3590$, $R^2=0.36$, test for regression slope: df=40; $t=-4.78$; $P<0.0001$).

(−30.0, −60.0, 15.0), t=4.47} demonstrated a significant negative correlation with age (Fig. 3). Even if the analysis was done on voxels with FA values higher than 0.35, to examine more anisotropic WM areas, the results were essentially unchanged (data not shown).

3.1.3. Correlational analysis between FA values and clinical factors in schizophrenics

There was a significant negative correlation between FA values and duration of illness in widespread WM areas (Fig. 4), while there was no significant correlation of FA values with age of onset, duration of hospitalization or daily dose of antipsychotic drugs (data not shown).

3.2. ROI analyses

3.2.1. ROI-based correlational analysis in both schizophrenics and controls

First, we constituted a General Linear Model putting diagnosis as a fixed factor and age, IQ and relative WM volume as covariates. F values (significance probabilities) were as follows; diagnosis: 10.8 (P=0.001), age: 26.1 (P<0.001), IQ: 0.029 (P=0.865) and relative WM volume: 16.6 (P<0.001). Then, we added diagnosis-by-age interaction into the model. F values (significance probabilities) changed as follows; diagnosis: 2.34 (P=0.130), age: 27.8 (P<0.001), IQ: 0.059 (P=0.809), relative WM volume: 14.1(P<0.001) and diagnosis-by-age interaction: 7.08 (P=0.009). Effect of IQ was not significant in both models. There was a significant diagnosis-by-age interaction effect.

3.2.2. ROI-based correlational analysis in controls

Pearson's correlation coefficients (significance probabilities of the test of significance of the correlation: two-tailed) of mean WM FA value with age, IQ and relative WM volume in controls were as follows; FA vs. age: −0.287 (P=0.065), FA vs. IQ: −0.108 (P=0.496) and FA vs. mean WM volume: 0.481 (P=0.001). Only positive correlation between mean WM FA value and relative WM volume was statistically significant.

3.2.3. ROI-based correlational analysis in schizophrenics

Pearson's correlation coefficients (significance probabilities of the test of significance of the correlation: two-tailed) of mean WM FA value with clinical factors in schizophrenics were as follows; FA vs. age: −0.702 (P< 0.001), FA vs. duration of illness: −0.603 (P<0.001), FA vs. age of onset: −0.305 (P=0.049), FA vs. total daily dose of antipsychotics: 0.110 (P=0.489), FA vs. duration of hospitalization: −0.172 (P=0.277), FA vs. IQ: −0.064 (P=0.686), FA vs. relative WM volume: 0.421 (P=0.006). Significant positive correlation was observed between mean WM FA value and relative WM volume. Fig. 5 shows a scatter plot between age and mean WM FA value in controls and schizophrenics. Fig. 6 shows a scatter plot between duration of illness and mean WM FA value in schizophrenics. Significant negative correlations were observed between mean WM FA value and age (or duration of illness).

4. Discussion

In this study, we obtained three main findings; 1) lower FA values in schizophrenic patients compared with controls in WM areas including frontal and temporal WM, bilateral uncinate fasciculi (external capsules) and cingulum bundles and genu and splenium of corpus callosum, 2) age-related reductions of FA value in the widespread WM were more prominent in schizophrenics than in controls, and 3) a negative correlation between FA value in the widespread WM and duration of illness in schizophrenics.

Recent studies demonstrated age-related FA decline in normal individuals occurred in the prefrontal WM, while temporal WM were relatively preserved (Pfefferbaum et al., 2005; Salat et al., 2005). However, in this study, negative age-dependent effects were observed only in the lenient statistical threshold in the FA values of restricted areas of the WM in controls. This could be explained by the fact that all our subjects were under the age of 60, relatively less old compared to the participants of normal aging studies.

We replicated the results of the most of the previous studies, decreased FA values in the WM of schizophrenics. In the earlier studies concerning FA values in WM of patients with schizophrenia, an inherent abnormality in WM was expected to be detected since the decrease of FA values in the WM of the schizophrenic brain was assumed to occur as neurodevelopmental impairments before onset of the illness. Several studies demonstrated that schizophrenics had reduced FA value in the prefrontal WM (Buchsbaum et al., 1998), prefrontal and parieto-occipital WM (Lim et al., 1999), splenium of the corpus callosum (Agartz et al., 2001) and adjacent occipital WM (forceps major) (Agartz et al., 2001), left uncinate fasciculus and bilateral arcuate fasciculus (Burns et al., 2003), bilateral cingulum bundles (Kubicki et al., 2003). Some of them indicated that the reduction of FA values in schizophrenics might occur independently of reduction of the white matter volume. Although some studies reported no significant FA changes in schizophrenics (Steel et al., 2001; Foong et al., 2002), most studies with chronic

schizophrenia demonstrated lower FA values in schizophrenia (Kanaan et al., 2005). A few DTI studies have examined first episode patients (Price et al., 2005; Szeszko et al., 2005). Szeszko et al. found FA decrease in the left internal capsule and left-hemisphere WM of the middle frontal gyrus and posterior superior temporal gyrus of first-episode schizophrenics and schizoaffective disorder patients, however, the decrease was less pronounced compared with results of the majority of the studies in chronic schizophrenics. On the other hand, Price et al. reported that there was no FA decrease in the corpus callosum of patients with first-episode schizophrenia. They suggested that FA reduction in schizophrenia might reflect neuropathological abnormalities, which may occur after the onset of the disease and could be progressive. Our results, 1) age related FA reduction was more prominent in schizophrenics than controls, and 2) duration of illness was related to FA reduction in schizophrenics, suggest that changes of FA value in schizophrenia are attributable, at least in part, to progressive neuropathological changes after onset of the illness.

Contrary to our results, a previous DTI study demonstrated 'positive' correlation between age and FA in schizophrenics (Jones et al., 2006). They measured FA values of WM tracts captured from tractography, and they set seedpoints of the tracts manually from one slice of FA images. Such methods might overlook general decline of FA values in the WM. Their mean FA values (average of 8 WM tracts in each subjects) were around 0.4, which was relatively higher than those of our study {our mean FA value of entire WM was 0.35 + 0.01 (mean + S.D.)}. To simulate the analysis of the previous study, we additionally performed an analysis setting masking threshold for FA values of 0.35. As a result, the significant negative correlation remained to be present even in more anisotropic WM areas.

Previous pathological studies demonstrated microscopic abnormalities of the WM in schizophrenia such as decreased expression of myelin and oligodendrocyte-related genes, the decrease in density of oligodendrocytes (Hof et al., 2002), damage of myelin sheath lamellae (Uranova et al., 2001) and maldistribution of interstitial neurons (Akbarian et al., 1996) in prefrontal WM of the brains of schizophrenic patients. Further, a previous longitudinal MR study demonstrated progressive atrophy of the white matter in schizophrenics (Ho et al., 2003). Given these previous findings and ours, it seems likely that age-dependent FA decrease, but not increase, occurs in schizophrenic brains.

As well as a negative correlation with age, FA values of schizophrenics showed negative correlation with duration of illness but not with age of onset or daily dose of antipsychotics. The facts seem to support the hypothesis that FA reduction in schizophrenia might be associated with neuropathological abnormalities which may emerge, at least in part, after the onset of the disease and could be progressive. Further, the spatial distribution of age-related FA reduction in schizophrenics was different from those of normal individuals in previous studies that demonstrated preserved temporal white matter (Pfefferbaum et al., 2005; Salat et al., 2005). Such different distributions suggest that FA changes in schizophrenics might be associated with disease progression rather than merely exaggerated aging effects. However, it is difficult for neuroimaging studies, even for longitudinal studies, to discriminate disease progression from aging effects. The correlational study between DTI findings and pathological findings should be conducted to clarify whether reduction of FA values in schizophrenics reflect pure disease progression or merely exaggerated aging effects.

Several limitations should be considered in our study. First, our study is a cross-sectional study. To confirm progressive pathological process in the WM of the patients of schizophrenia, longitudinal studies should be conducted. Second, IQ score was not matched between groups, i.e., mean IQ score was significantly lower in schizophrenics in our samples. O'Sullivan et al. (2004) reported DTI measures were correlated strongly with cognitive decline in elderly. Thus, it could be problematic whether age-related FA decrease in our study was reflected by cognitive decline. However, no significant correlation was observed between mean WM FA values and IQ in our sample. Also, regarding schizophrenia, it has been hypothesized that most cognitive change takes place early in their psychotic episodes and it remains relatively stable through long term in the illness (Hoff et al., 2005). Hence, at least from our data, we cannot attribute age-related FA decline in schizophrenia to IQ changes. Third, the issue of partial volume effect should be addressed. In schizophrenia, progressive WM atrophy has been reported in the previous studies (Ho et al., 2003). Due to the atrophy, it is possible that the voxels located in the border of the WM and other tissues in schizophrenics were estimated as having lower FA values. However, we minimized the problem by using the high dimensional warping algorithm, threshold masking for FA values and adopting relative WM volume as a nuisance variable. Another issue is the possible effect of long-term medication with antipsychotics. Although daily dose of antipsychotics was not correlated with FA values in schizophrenics, we could not estimate accurate cumulative doses of antipsychotics

throughout the duration of illness. Several morphological MR studies and animal studies suggested that the administration of antipsychotics could affect brain morphology (Wang et al., 2004; Lieberman et al., 2005). It is possible that long-term medication with antipsychotics also affects microstructure of the WM in schizophrenics. The longitudinal animal studies may clarify this issue.

In conclusion, we confirmed decreased FA in schizophrenics, compared to controls in the widespread WM areas in a Japanese sample. We found that age-dependent FA decline was more pronounced in chronic schizophrenics compared to controls, and that such FA decline was significantly correlated with duration of illness in patients. These observations suggest that decreased FA values in schizophrenia might be attributable, at least in part, to progressive changes in the WM after the onset of the illness.

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Manuscript Draft

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Title: Personality in schizophrenia assessed with the Temperament and Character Inventory (TCI)

Article Type: Research Article

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Keywords: schizophrenia; personality; temperament; character; gender difference

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Abstract: The Temperament and Character Inventory (TCI) is a well-established self-report questionnaire measuring 4 temperament and 3 character dimensions. However, surprisingly few studies have used it to examine the personality of patients with schizophrenia, and none in Japan. Moreover, possible gender differences in personality among patients with schizophrenia have not been well documented. We administered the TCI to 86 Japanese patients with schizophrenia and age- and gender-matched 115 healthy controls to characterize personality traits in patients with schizophrenia and to examine their relationships with clinical variables, particularly gender and symptoms. Compared to controls, patients demonstrated significantly lower novelty seeking, reward dependence, self-directedness and cooperativeness, and higher harm avoidance and self-transcendence. Male patients showed even more pronounced personality alteration than female patients when both of them were compared to healthy people. Personality dimensions were moderately correlated with symptom dimensions assessed by the Positive and Negative Syndrome Scale (PANSS). These results, together with prior findings in several other countries, suggest that

schizophrenia patients have a unique personality profile which appears to be present across cultures and that the greater alteration of personality in schizophrenia males might be related to their poorer social and community functioning.

Cover Letter

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May 11, 2007

Re: Personality in schizophrenia assessed with the Temperament and Character Inventory (TCI) (PSY-D-07-00096)

Dear Prof. Buchsbaum:

Thank you for providing us with an opportunity to resubmit our manuscript. We are also very grateful to the anonymous referee for valuable comments. According to the comments, we have revised our manuscript. Please refer to the answers to the referees on separate sheets. I hope that the revised version will be suitable for publication in *Psychiatry Research*.

We are looking forward to hearing from you in due course.

Sincerely,

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Answers to the editors' requirements:

Comment 1 In addition to the points raised by the reviewers, please carefully review the Guide to Authors on our website. It would be also be useful for you to review the articles contained in the sample issue on our website for examples of title page format, heading typography, and other style features.

Answer: According to the editors' comments, we have revised the manuscript as carefully as we can, based on the stylistic requirements of the *Journal*.

Comment 2 We also thought the ms needs to be shortened. You can easily combine Tables 1 and 2. It also appears that the figure duplicates the data in Table 3. Please chose one or the other.

Answer: According to the comment, we have combined the previous Tables 1 and 2 into a new table, Table 1, and removed the data on male vs. female comparisons from Table 3 since the similar data are, as pointed out by the editors, also presented in Fig. 1. Descriptions on the gender difference in the Results section have been modified accordingly (L4-19, P11).

Answers to the reviewer #1:

Comment 1 The introduction might say more about what exactly studies have previously found. What symptoms have been linked with what personality dimensions and what was made of that by previous authors? This should be spelled out as it is the context in which the authors should later interpret the results. The literature on this subject could also be more broadly noted and cited.

Answer: According to the reviewer's comment, we have increased the descriptions on what previous studies have found regarding the following issues: relationships between symptoms and personality dimensions (L14-20, P4), variability of personality as assessed with the TCI across cultures (L18-21, P3), and various aspects of gender difference unfavorable to male patients (L3-6, P5). Furthermore, several relevant references have been added to the Introduction section.

Comment 2 The introduction might say more about what specific previously unaddressed or under studied questions this study seeks to explore. What is the gap these finding intend to fill besides just using another instrument.

Answer: The questions we had considered unaddressed or under studied were gender difference and cross-cultural comparisons of personality in schizophrenia, and comparisons of TCI and NEO-FFI findings in schizophrenia. In addition, we thought that the relationships between symptoms and personality in schizophrenia remain to be further examined. According to the helpful comment, we have clearly stated the gaps this study intended to fill regarding these questions (L21, P3 to L1, P4; L9-13, P4; L20, P4 to L1, P5; L6-8, P5).

Comment 3 The introduction could include they study hypotheses. What was anticipated?

Answer: According to the helpful comments, we have added 3 hypotheses that correspond to the aims of this study (L13-19, P5).

Comment 4 I would not use the word deviant when referring to the personality of the sample. "Deviant" can have a very negative connotation, implying in some senses criminality or antisocial tendencies which certainly is not what the authors intend.

Answer: We have now realized that "deviant" has a very negative connotation which we were at first unaware of. Therefore, we have changed the word "deviant" into "altered" or "unique", and "deviance" into "alteration" throughout the manuscript.

Comment 5 The discussion could be condensed and re-organized around the study hypotheses once laid out in the introduction.

Answer: According to this comment, we have re-organized the discussion section, focusing on the 3 hypotheses laid out earlier. Furthermore, we have explicitly

described whether the hypotheses have been supported (L13, P15; L17-19, P15; L5-7, P17). The speculative discussion on causal relationships between personality and development of schizophrenia has been deleted.

Comment 6 Results could also be linked back more carefully to the results of studies using other methods of personality assessment as noted in the introduction.

Answer: According to the helpful comment, we have added the detailed descriptions on comparisons between the present TCI results and previous findings from NEO studies in the Discussion section (L19, P14 to L13, P15).

*** Title Page showing full Author and Address Details**

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