manually, following the procedure used by Haznedar et al. (2004) for outlining the ACG. Outlining began ventrally with the plane showing the appearance of the cingulate sulcus and ended dorsally (35–41 planes higher) with the plane showing the disappearance of the corpus callosum. Finally, by applying intensity filters to remove white matter components, the gray matter components of the ACG (i.e., the ACC) were extracted for volumetric analysis (Fig. 1). In addition, estimation of whole brain volume (WBV) was obtained after the automatic brain segmentation procedure carried out by SPM2.

DTI in the anterior cingulum

FA was defined as the standard deviation of eigenvalues from the mean eigenvalue, normalized by square norm of eigenvalues. Parametric images of FA were calculated using a computer program (DTI-Studio, version 2.40; Johns Hopkins University, Baltimore, USA). The FA in each anterior cingulum was measured using DTI-Studio. ROIs (round, diameter=4 pixels) were placed on two slices inferior to the most dorsal plane in which the middle cingulum was displayed. In order to place ROIs exactly onto the anterior cingulum, ROI placement was performed under the guidance of simultaneously displayed color maps. To check the validity of ROI placements further, we performed fiber tracking from each ROI and confirmed the visualization of cingulum extending from each ROI (Fig. 2).

Paracingulate/Cingulate morphology

On the three dimensional images we used for ACC volumetry, the macroscopic pattern of ACG sulcal morphology was classified in respect of the presence of a PCS and the continuity of the CS, using the method applied by Yücel et al. (Yücel et al., 2002b, 2003). In classifying the PCS, based on the presence or absence of the PCS and its antero-posterior length, three categories of morphologic variations were defined: prominent PCS, present PCS and absent PCS (Fig. 3). To classify CS variations, continuous and discontinuous types were defined based on the absence or presence, respectively, of a clear interruption in the course of the CS.

Intrarater and interrater reliability for morphological measurements

All of the following structural measurements were performed by the first author (HF). To determine the reliability of ACG measurements, 10 subjects were randomly selected and measurements were performed independently by two raters (HF, MS) on these 10 subjects. Intrarater reliability was assessed by one rater (HF), and interrater reliability was assessed by introducing the second rater (MS). Both raters were blinded to participant details, including the study group and the results of neuropsychological tests, during the measurement. The intraclass and interclass correlation coefficients for the re-assessment of the left/right ACC volumes were 0.96/0.95 and 0.95/0.92, respectively. The intrarater and interrater reliability for the assessment of left/right FA in the defined ROIs were 0.95/0.96 and 0.93/0.95, respectively. Both intrarater and interrater reliability for the classifications of CS continuity/PCS morphology were established using 10 randomly chosen cases (20 hemispheres), with K values of 0.96/1.00 and 0.95/0.91, respectively. These results suggest that the reliability of all the morphological measures was satisfactory.

Clinical and basic neuropsychological assessments

Subjects were assessed when they were in a clinically stable phase. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). To estimate subjects' general intelligence quotient (IQ), the vocabulary and block design subtests of the Japanese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were administered.

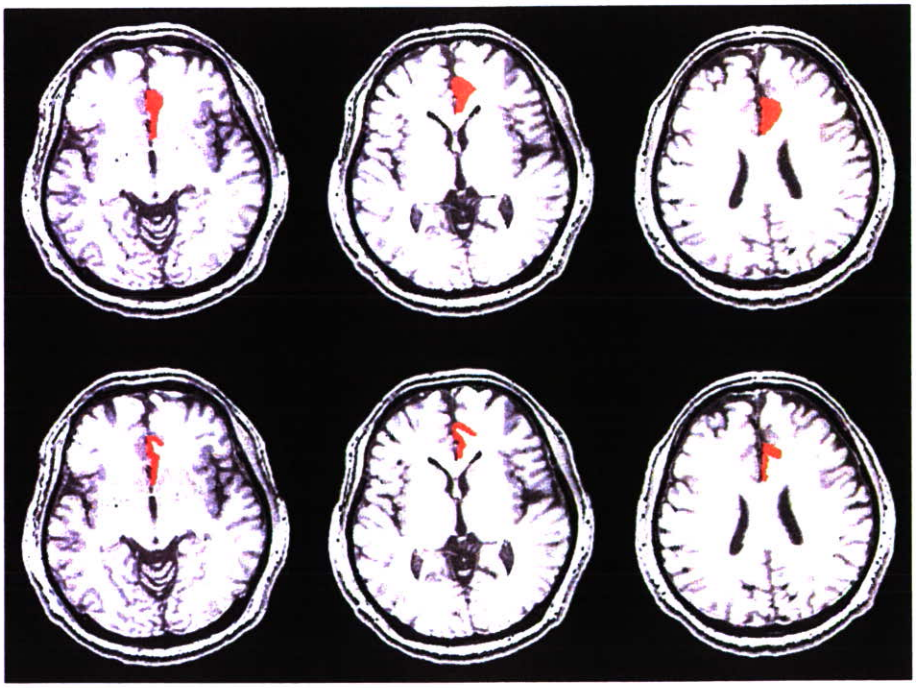

Fig. 1. Upper panel: manually traced anterior cingulate gyrus including subcortical white matter. Lower panel: gray matter components of the upper images.

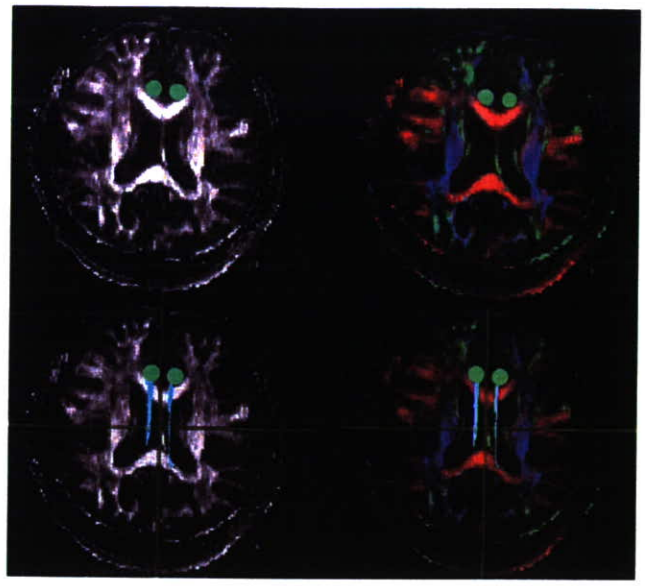

Fig. 2. Left upper panel: a fractional anisotropy (FA) map of a representative subject, the regions of interests (ROIs) in the anterior cingulum are also shown (green circle). Right upper panel: color maps corresponding to the images in the left panel. Color maps are computed using the absolute values of the *X*, *Y* and *Z* components from the eigenvector from a given diffusion tensor. *X*, *Y* and *Z* components were visualized with red, green and blue colors, respectively. In the lower images, fiber-tracked images of the cingulate bundles were mapped and superimposed onto the corresponding upper axial images (turquoise). For fiber tracking, tracking from all the pixels inside the brain was performed, and tracking results that penetrated the manually segmented ROIs on the basis of the known anatomic distributions of tracts were assigned to specific tracts. Propagation in each fiber tract was terminated if a voxel with a FA value of less than 0.2 was reached.

Estimated verbal and performance IQ scores were obtained by transforming each subtask score, corrected for age, into *T* scores. To control for basic visuoperceptual ability with facial stimuli, a short version of the Benton Facial Recognition Test (BFRT) was administered (Benton et al., 1983).

Emotion attribution tasks

To examine various levels of social cognitive abilities in the subjects, we administered the Perception of Affect Tasks (PAT) (Rau, 1993), as applied in our previous study (Yamada et al., 2007). This task evaluates subjects' ability of attributing emotions to facial expressions and to story protagonists in complex social situations. The task consists of four subtasks designed to assess verbal, visual and verbal–visual processing separately. In subtask 1, participants were presented with short stories describing emotional situations. From a list of seven emotion labels (happiness, sadness, fear, anger, disgust, surprise, and neutral), they were asked to choose the one that best described the feeling of the main protagonist in each situation (matching the *v*erbal description of a *s*ocial situation with emotional *labels*; S (v) with Label). Subtask 2 is a matching task of emotional facial stimuli with emotional verbal labels. Presented with emotional facial stimuli selected from the Picture of Facial Affect series (Ekman and Friesen, 1976), subjects were requested to select the best verbal labels from the seven alternatives (matching emotional *faces* with emotional *labels*; Face with Label). In subtask 3, the participants were again presented with the same story series as in subtask 1 and were requested to choose the emotional facial expression, from the same list of seven, that best described the feeling of the main protagonist in each situation (matching *v*erbal descriptions of *s*ocial situations with emotional *faces*; S (v) with Face). Finally, in subtask 4, the participants were provided with seven photographs of social situations, in which the main human figures conveyed one of the seven emotions. The faces of these figures were erased or were not observable. Participants were presented with facial stimuli as in subtask 2 and requested to choose the human figure that best described the emotional facial stimuli presented (matching emotional *faces* with non-verbal *s*ocial situations; Face with S (nv)). Each subtask consisted of 35 stimuli, five items for each of seven emotions.

Statistical analyses

All statistical analyses were performed in SPSS version 12.0. Demographic data were compared using a two-tailed *t*-test. Between-group differences in ACC volumes and FA in the anterior cingulum were assessed by a repeated measures ANCOVA; laterality of the ROIs was the repeated measure, and age was included as a nuisance covariate. Whole brain volume (WBV) was also included as a covariate in the analysis of ACC volumes. As in the studies by Yücel et al. (Yücel et al., 2003), McNemar's test for symmetry was used to test whether the number of cases of PCS asymmetry in one direction was counterbalanced by an equal number of cases with an asymmetry in the other direction. In addition, the effect of diagnostic group on PCS morphology was further examined using chi-squared analyses. The effect of diagnostic group on CS continuity was also examined using a 2×2 χ^2 analysis. Group comparisons of performance in each of the four PAT subtasks were performed using two-way analyses of variance (ANOVA), with group (schizophrenia and healthy subjects) as a between-subject factor and emotion category (happiness, sadness, fear, anger, disgust, surprise and neutral) as a within-subject factor. $P<0.05$ is regarded as significant.

Structure–structure correlations were investigated both for patients and normal subjects. As well, structure–psychopathology, and structure–social cognition correlations were investigated in the patient group. Pearson's correlation coefficients were used if an initial exploration of the data set suggested normal distribution of the data. As a result, PCS/CS morphological measures were found to be not normally distributed; thus we applied an unpaired *t*-test to investigate the relationships between CS morphological types (binary) and other variables and applied Spearman's correlation coefficient to investigate the relationships between PCS morphological types and other variables.

Due to the relatively small sample size and exploratory nature of this study, correction for multiple comparisons was not applied, and an uncorrected *P*-value of 0.05 was regarded as the statistical threshold of significance for all correlational analyses.

Results

Demographic and basic neuropsychological data

Demographic information is shown in Table 1. There were no significant differences in age, education and estimated verbal and performance IQ scores between schizophrenia patients and healthy

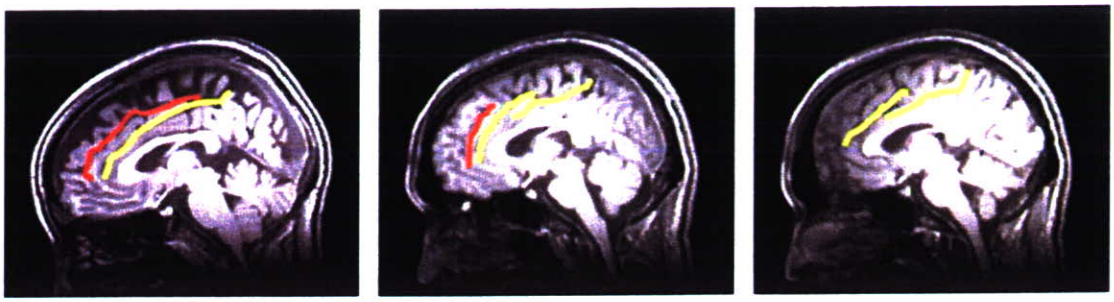

Fig. 3. MR images and corresponding line drawings of right hemispheres illustrating the variations in paracingulate morphology and cingulate sulcus (CS) continuity. The hemisphere on the left shows a prominent paracingulate sulcus (PCS) and a continuous CS, whereas those in the middle and on the right show a present PCS/interrupted CS and absent PCS/interrupted CS, respectively.

subjects. There was also no significant difference between schizophrenia patients and healthy subjects in BFRT scores.

Brain morphometric analysis

ACC volumetry

Supporting previous reports (Haznedar et al., 2004; Suzuki et al., 2002; Yamasue et al., 2004), group differences in whole brain volume were not found between healthy subjects (1129 cm^3, SD=134 cm^3) and schizophrenia patients (1120 cm^3, SD=107 cm^3). Compared to healthy subjects (right/left hemisphere; 6385/6622 mm^3, SD=589/650 mm^3), schizophrenia patients (right/left hemisphere; 5912/5993 mm^3, SD=733/810 mm^3) had smaller anterior cingulate cortices bilaterally (ANCOVA, age and whole brain volume as covariates, group effect, $F(1,42)=8.084$, $P=0.007$, no group×hemisphere interaction; Fig. 4A).

DTI in the anterior cingulum

Consistent with previous findings (Sun et al., 2003; Kubicki et al., 2003; Wang et al., 2004), schizophrenia patients (right/left hemisphere; 0.53/0.53 SD=0.07/0.06) had decreased FA in the bilateral anterior cingulum compared to healthy subjects (right/left hemisphere; 0.60/0.66 SD=0.09/0.06) (ANCOVA, age as a covariate, group effect, $F(1,43)=11.63$, $P=0.001$, no group×hemisphere interaction; Fig. 4B).

PCS/CS morphology

The PCS classifications across each hemisphere of each diagnostic group can be seen in Table 2A. McNemar's test revealed significant asymmetry in the control group ($\chi^2(3)=8.364$; $P=0.039$) but not in the patient group ($\chi^2(3)=0.533$; $P=0.921$), indicating a biased distribution of PCS morphology in healthy subjects, but not in those of schizophrenia patients. There was a significant difference in PCS morphology between the two groups, in the left hemisphere only: the schizophrenia patients were less likely than the control group to have a prominent PCS in the left hemisphere ($\chi^2(2)=7.018$; $P=0.030$). Regarding CS morphology, the proportions of participants with either a continuous or interrupted CS can be seen in Table 2B. There was a significant difference in continuity between the two groups, in the left hemisphere only: the schizophrenia patients were more likely than the healthy subjects to have an interrupted CS in the left hemisphere ($\chi^2(1)=8.231$; $P=0.004$).

Table 1
Demographic and clinical characteristics of participants

	NC ($N=20$)		SCZ ($N=26$)		Statistics	
	Mean	SD	Mean	SD	t ($df=44$)	P
Age (years)	37.8	7.4	37.1	7.6	0.13	NS
Sex (male/female)	10/10		13/13		–	–
Handedness (left/right)	1/19		1/25		–	–
Education years	14	2.7	13.7	2.4	0.15	NS
Age at onset (years)	–	–	26.6	7.9	–	–
Duration of illness (years)	–	–	10.1	7.9	–	–
Drug (mg/day, haloperidol equivalent)	–	–	13.0	8.1	–	–
Dose years	–	–	47.6	38.6	–	–
PANSS Positive	–	–	15.7	6.4	–	–
PANSS Negative	–	–	16.3	6.2	–	–
PANSS General	–	–	32.4	9.6	–	–
VIQ	104.7	15.5	97.3	15.8	1.63	NS
PIQ	107.8	12.7	99.8	15.1	1.89	NS
BFRT	47.2	4.0	45.3	5.7	1.24	NS

Abbreviations: PANSS=Positive and Negative Syndrome Scales, VIQ=verbal intelligence quotient, PIQ=performance intelligence quotient, BFRT=The Benton Facial Recognition Test; NC=normal control, SCZ=schizophrenia.

Behavioral measures

Perception of Affect Task

Performance in all subtasks was significantly affected by group (S (v) with Label: $F(1,44)=4.40$, $P=0.042$; Face with Label:$F(1,44)=6.71$, $P=0.013$; S (v) with Face: $F(1,44)=16.97$, $P<0.001$; Face with S (nv): $F(1,44)=12.14$, $P<0.001$), with schizophrenia patients performing worse than healthy subjects. None of the group by emotion interactions attained statistical significance across subtasks (in all comparisons $P>0.05$).

Correlation analyses

Structure–structure relationship

In either schizophrenia or healthy subjects, no significant statistical correlation was found among ACC volume, FA in the anterior cingulum and PCS/CS morphology within each hemisphere.

Medication effect

Neither current dosage nor "dose years" (cumulative amount of neuroleptic exposure) showed a significant correlation with any morphological measures investigated.

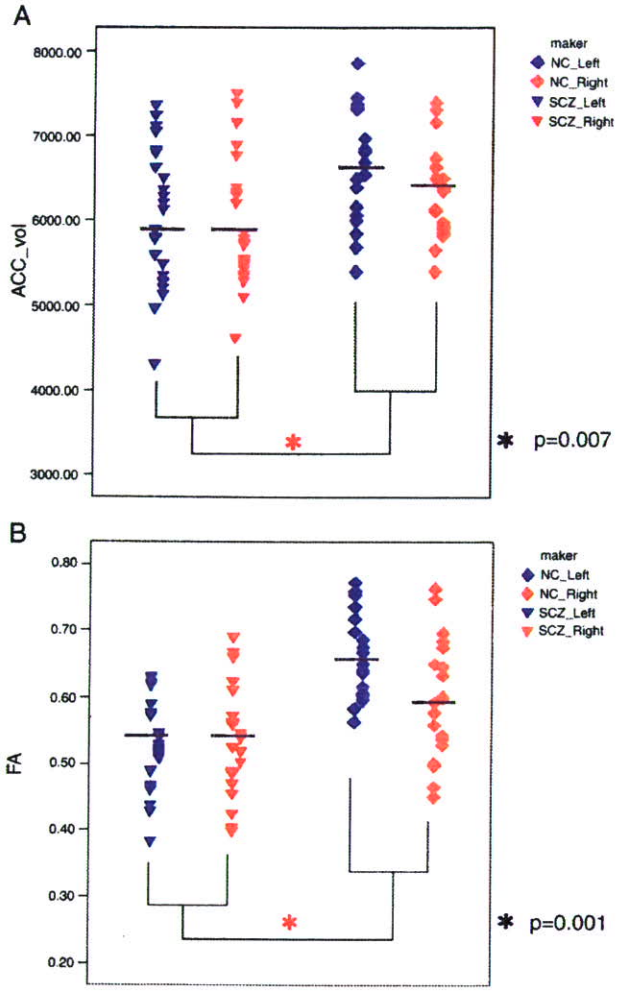

Fig. 4. (A, B) Volumetric (A) and FA (B) measurements of the anterior cingulate in normal control subjects and patients with schizophrenia. Abbreviations: FA=fractional anisotropy, ACC_vol=anterior cingulate cortex volumes, NC=normal, controls, SCZ=schizophrenia subjects.

Structure–psychopathology relationship

Significant statistical correlation was found between right ACC volume and positive symptoms ($P=0.046$), and between left PCS morphology and negative symptoms ($P=0.024$) (Table 3). No other significant relationships between ACG structural measures and symptom ratings were demonstrated.

Table 2A
ACG morphological classifications: paracingulate morphology

	NC ($N=20$)			SCZ ($N=26$)		
	Prominent (%)	Present (%)	Absent (%)	Prominent (%)	Present (%)	Absent (%)
Left hemisphere	70	20	10	31	42	27
Right hemisphere	30	60	10	35	35	30

Data are proportions (%) of AC classifications. Abbreviations: NC=normal control, SCZ=schizophrenia.

Table 2B
ACG morphological classifications: cingulate sulcus continuity

	NC ($N=20$)		SCZ ($N=26$)	
	Continuous (%)	Interrupted (%)	Continuous (%)	Interrupted (%)
Left hemisphere	90	10	50	50
Right hemisphere	85	15	81	19

Data are proportions (%) of AC classifications. Abbreviations: NC=normal control, SCZ=schizophrenia.

Structure–social cognition relationship

Significant positive correlation was found between left or right ACC volume and Face with Label, S (v) with Face, or Face with S (nv) (Table 4), indicating that the smaller the volume of the left or right hemispheres, the poorer the performance of these subtasks. As well, comparison of the two groups classified by CS (continuous-CS vs. interrupted-CS) using an unpaired t-test revealed that patients with a continuous left CS performed S (v) with Label more accurately than those with an interrupted left CS, indicating an association between left CS morphology and this subtask. No other significant relationships between ACG structural measures and task performance were demonstrated.

Discussion

This is the first study to simultaneously examine ACC volume, FA in the anterior cingulum and surface morphology of the ACC in patients with schizophrenia. As well, the relationship among these three morphological measures and their associations with psychopathology and social cognitive function has been explored. The major findings of this study are:

(a) patients with schizophrenia have smaller bilateral ACC volume and decreased FA in the anterior cingulum compared with healthy controls. They are also less likely to have a well-developed PCS and more likely have interruptions in the course of the CS in the left hemisphere;
(b) there appears to be no interrelationship among the three morphological measures of ACG abnormality (i.e., ACC

Table 3
Relationships between structural abnormalities in the ACG and both psychopathology and Perception of Affect Task scores in patients with schizophrenia

	Left ACC	Right ACC	Left FA	Right FA	Left CS	Left PCS
PANSS Positive	NS	$r=-0.412$*	NS	NS	NS	NS
PANSS Negative	NS	NS	NS	NS	NS	$r=0.441$*
Subtask 1	NS	NS	NS	NS	$t=2.899$**	NS
Subtask 2	$r=0.399$*	$r=0.415$*	NS	NS	NS	NS
Subtask 3	$r=0.433$*	$r=0.480$*	NS	NS	NS	NS
Subtask 4	NS	$r=0.446$*	NS	NS	NS	NS

*$P<0.05$; **$P<0.01$.
Abbreviations: ACC=anterior cingulate cortex, FA=fractional anisotropy, CS=cingulate sulcus, PCS=paracingulate sulcus.

Table 4
Perfomance of the Perception of Affect Task in normal and schizophrenia subjects

	NC (N=20)	SCZ (N=26)
	Mean score (SD), percent correct (%)	Mean score (SD), percent correct (%)
S (v) with Label	30.0 (2.6), 85.6	27.9 (4.3), 79.7
Face with Label	29.5 (2.7), 84.2	26.7 (4.0), 76.4
S (v) with Face	28.8 (3.6), 82.2	23.5 (4.7), 67.3
Face with S (nv)	29.2 (3.9), 83.5	23.6 (6.3), 67.4

Mean scores (SD) and percent correct of response (%) are presented.
Abbreviations: NC=normal control, SCZ=schizophrenia, S (v) with Label=matching the verbal description of social situation with emotional labels, Face with Label=matching emotional faces with emotional labels, S (v) with Face=matching verbal descriptions of social situations with emotional faces, Face with S (nv)=matching emotional faces with non-verbal social situations.

volume, FA in the anterior cingulum and PCS/CS morphology);

(c) social cognitive functions, as evaluated by the ability to attribute emotions to facial expressions and to story protagonists, were significantly compromised in patients with schizophrenia;

(d) different aspects of ACG abnormalities were differentially associated with psychopathology or social cognitive function in schizophrenia.

The present findings are generally consistent with previous studies. ACC volume reductions as well as decreased FA have been reported in patients with schizophrenia (Sun et al., 2003; Kubicki et al., 2003; Wang et al., 2004; Yamasue et al., 2004). Although the group by hemisphere interaction was not significant, effect size (partial eta-squared value ($\eta^2 p$)) was greater in the left than in the right for FA values ($\eta^2 p$=0.215/0.097). Such a lateralized pattern of cingulate pathology is consistent with a previous finding (Wang et al., 2004). Poor development of the PCS and an interrupted course of the CS in the left hemisphere have been indicated (Yücel et al., 2002b, 2003). However, in contrast to our initial assumption, we could not find inter-relationships among these different morphological measures, suggesting that the ACG pathology observed in schizophrenia is not unitary.

ACC volumes are known to be associated with PCS/CS patterns in normal healthy subjects (Paus et al., 1996; Fornito et al., 2006a). Although it has not been investigated directly, underlying white matter microstructure might also be associated with the PCS/CS patterns, considering the role of tension of regional white matter in the formation of sulcal/gyral patterns (Van Essen, 1997). Thus, if the ACG abnormality in schizophrenia is determined by a single pathological process involving PCS/CS patterning during early and late gestation (Chi et al., 1977; Armstrong et al., 1995), it is expected that the ACC volumetric, cingulum FA and PCS/CS pattern measures are mutually correlated. However, we did not find such correlations. The lack of such intercorrelations might be due to our relatively small sample size; an alternative possibility is that the pathological processes of ACG occur in multiple phases of neurodevelopment in schizophrenia. Different structural aspects (macroscopic sulcal pattern, ACC volumes, and cingulum microstructures) would be affected at different weights depending on the nature of the putative neuropathological processes and their timing in the process of neurodevelopment.

Gray matter maturation including synaptic pruning occurs after birth through childhood to adolescence. Thus, the pathological events in any timing of gray matter maturation would affect regional gray matter volume changes in schizophrenia. Indeed, in childhood-onset schizophrenia subjects, abnormal patterns of cortical development were demonstrated by longitudinal MRI studies (Sporn et al., 2003). As well, after disease onset, neuroleptic medication would also affect regional gray matter volumes (Lieberman et al., 2001).

Less is known regarding the nature of the white matter pathology of schizophrenia. Myelination (myelin is generally assumed to be major barrier to diffusion in white matter tracts (Kubicki et al., 2005)) still occurs in the second decade of life, especially in frontal and temporal lobes (Benes et al., 1994). Any pathological processes disturbing initial myelination process or turnover of once-formed myelinated white matter could affect the regional white matter FA measures in later life. As a candidate for such white matter pathology, several reports have demonstrated the pathology of oligodendroglia, which form myelin sheaths, in schizophrenia (Uranova et al., 2001, 2004; Hakak et al., 2001; McCullumsmith et al., 2007)

Consistent with our previous study (Yamada et al., 2007) and studies reporting social cognitive impairment in schizophrenia (Brune, 2005; Frith, 2004; Doody et al., 1998), the behavioral tasks revealed that the ability of patients with schizophrenia to attribute emotions to facial expressions and to story protagonists was significantly compromised. However, no previous studies have examined the relationships between structural abnormalities in the ACG and impairments in social cognitive function in schizophrenia. In our study, a significant positive correlation was found between the left or right ACC volumes and Face with Label, S (v) with Face, or Face with S (nv) (all of which use emotional facial expressions as stimuli), indicating that better performance of these subtasks could be expected with larger ACC volume. This result is in accordance with the finding of an association between ACC volume and social cognitive performance in patients with frontotemporal dementia (Lough et al., 2006). We also found a relationship between left CS morphology and S (v) with Label (which includes only verbal stimuli), indicating that patients with an interrupted left CS perform this subtask less accurately. Although there are no reports investigating lateralized ACG function in association with verbal or non-verbal presentation of social cognitive tasks, CS development in the dominant hemisphere may be specifically associated with the processing of social signals in verbal terms. Early formation of CS morphology might have substantial impact on both verbal and non-verbal social cognition ability in later life. However, if the impact of later pathology affecting ACC development in schizophrenia were much larger, it would have masked the effect of CS morphology on social cognition ability, except for that with verbal terms. The reason why social cognition ability in verbal terms is more impaired in patients with interrupted CS is unclear, but one possibility is that such ability is not very plastic and is underpinned by relatively hard-wired connections between left ACC and language areas in the dominant hemisphere. Finally, FA in the anterior cingulum was not associated with any social cognitive variables in our study. Nestor et al. (2004) reported a relationship between FA in this region and performance on the Wisconsin Card Sorting Test, which they considered to reflect dysfunction of the

dorsolateral prefrontal cortex. The anterior cingulum is the group of fibers connecting the ACC to other frontal regions and limbic structures (Mufson and Pandya, 1984); thus, pathology of the anterior cingulum could be associated with, for example, executive dysfunction or episodic memory, rather than social cognitive functions. Considering our results together, it appears that different neuropathologic manifestations of the ACG have impacts on different facets of social cognitive impairment in schizophrenia. Several studies have found an association between structural abnormalities of the ACG and negative symptoms (Suzuki et al., 2002; Yamasue et al., 2004; Takahashi et al., 2002; Paillere-Martinot et al., 2001) or severity of hallucinations (Noga et al., 1995); however, other studies have failed to identify this association (Sigmundsson et al., 2001). In the present study, structural abnormalities in the ACG were shown to be associated with psychopathology in patients with schizophrenia. Right ACC volume was correlated with positive symptoms, whereas left PCS morphology was correlated with negative ones. The latter finding is interesting in light of the studies by Fornito et al. (2004, 2006b), which have demonstrated relationships between "leftward PCS asymmetry" and working memory performance in both healthy controls and schizophrenia subjects. We did not divide them into different asymmetry categories as in the studies by Fornito et al. (2004, 2006b) due to the relatively small number of subjects in our study, neither did we investigate the working memory of the subjects. However, given the well established association between working memory deficits and negative symptoms in schizophrenia (Carter et al., 1996; Pantelis et al., 2001), and our findings, in corroborating with those by Fornito et al. (2004, 2006b), this sulcal variation could be a predictor of a later development of working memory deficit, prominent negative symptoms and poorer outcome of the disease, considering the fact that PCS morphology is determined very early in neurodevelopment. In respect of FA in the anterior cingulum, it was not associated with any psychopathological variables. Thus, in addition to indicating relationships between ACG pathology and psychopathology in schizophrenia, the current study also suggests that a different neuropathological pattern in the ACG can have a differential impact on psychopathology in schizophrenia.

Several limitations of our study should also be noted. First, the focus of this study was restricted to a single region of the brain. In schizophrenia, neuroanatomical abnormalities are not restricted to a single brain region. The impact of pathology in other brain regions, such as the amygdala or dorsolateral prefrontal cortex, on social–cognitive testing or psychopathology, was not taken into account in the present study. Second, statistically, a correction for multiple comparisons was not applied during correlation analyses. Thus, the reported relationships between structural abnormalities and social cognition or psychopathology should be regarded as preliminary findings.

In summary, this is the first study to simultaneously investigate ACC volume, FA in the anterior cingulum and surface morphology of the ACC in patients with schizophrenia. Although causal inferences should be considered cautiously in light of the limitations, our findings suggest that the ACG is disrupted in schizophrenia and that disruption in this region could be associated with social cognition and psychopathology in schizophrenia. It is also suggested that different dimensions of psychopathology and social cognitive function are associated in different ways with gray matter and sulcal morphological abnormalities in the ACG.

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Anterior and posterior cingulum abnormalities and their association with psychopathology in schizophrenia: A diffusion tensor imaging study

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Abstract

Evidence suggests that a disruption in limbic system network integrity and, in particular, the cingulate gyrus may play a role in the pathophysiology of schizophrenia. The cingulum bundles (CBs; posterior and anterior) are the most prominent white matter tracts in the limbic system, furnishing both input and output to the cingulate gyrus . In previous diffusion tensor imaging (DTI) studies, abnormal integrity has been demonstrated in the anterior CB portion, but not the posterior, in schizophrenia. As well, the relationships between the abnormalities of CB integrity and the psychopathology of schizophrenia remain to be elucidated. Using DTI acquired on a 3 T MRI machine, we examined fractional anisotropy (FA) in the anterior and posterior CBs of 42 patients with schizophrenia and 24 group-matched controls. Moreover, we investigated the relationships between CB abnormalities and the psychopathology of schizophrenia. Bilaterally reduced FA was demonstrated in both anterior and posterior CBs in schizophrenia patients. However, the pattern of FA reduction was different between anterior and posterior CBs: the reduction in FA was left-accentuated in anterior CBs, while no such lateralized abnormality was found in posterior ones. Finally, FA in posterior CBs correlated with positive symptom scores in patients with schizophrenia. These findings suggest that CB abnormalities in schizophrenia are not restricted to the anterior CB, but include the posterior as well. Pathology in the posterior CB would be one of the possible neural underpinnings of positive symptoms in schizophrenia.

Keywords: Schizophrenia; Cingulum bundle; Diffusion tensor imaging; Psychopathology

1. Introduction

The cingulum bundle (CB) is a white matter (WM) tract that underlies the cingulate cortex, connecting the cingulate cortex with multiple brain regions, including premotor and prefrontal regions, other cortical association regions, the thalamus, and medial temporal structures such as the presubiculum and parahippocampal gyrus (Mufson and Pandya, 1984). Disconnections between the cingulate gyrus and other regions may partly explain some of the symptoms and cognitive dysfunction in patients with schizophrenia (Cohen et al., 1999). Using

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diffusion tensor imaging (DTI), which provides a measure of WM organization, decreased fractional anisotropy (FA) in the anterior CB was reported in patients with schizophrenia (Sun et al., 2003; Kubicki et al., 2003; Wang et al., 2004).

Although no study has reported on decreased FA in the posterior CB in patients with schizophrenia, volume increases in the posterior cingulate WM have been reported (Mitelman et al., 2005). Thus, it is suggested that the posterior CB, in addition to the anterior CB, may have an important role in the pathophysiology of schizophrenia. In this study, DTI using a region of interest methodology was applied to examine WM integrity in different subregions of the CBs. In addition to the replication of previous findings in the anterior CB, we investigated whether abnormalities of posterior CB integrity are present or not. Moreover, we examined the relationships between FA in the CBs and the psychopathology of schizophrenia.

Table 1
Demographic and clinical characteristics of participants

	NC (N=24)		SCZ (N=42)		Statistics	
	Mean	SD	Mean	SD	t (df=64)	p
Age (years)	35.2	5.9	36.6	6.0	0.67	NS
Sex (male/female)	12/12		21/21		–	–
Handedness (left/right)	0/24		0/42		–	–
Education years	13.8	3.7	13.8	3.7	0.03	NS
Age at onset (years)	–	–	26.2	7.3	–	–
Duration of illness (years)	–	–	10.8	8.4	–	–
Drug (mg/day, haloperidol equivalent)	–	–	13.0	8.1	–	–
PANSS positive	–	–	14.9	6.2	–	–
PANSS negative	–	–	16.0	5.7	–	–
VIQ	107.2	10.3	100.7	10.0	−1.49	NS
PIQ	107.8	10.4	99.8	10.1	−1.81	NS

Abbreviations: PANSS = Positive and Negative Syndrome Scales, VIQ = verbal intelligence quotient, PIQ = performance intelligence quotient, NC = normal control, SCZ = schizophrenia.

2. Methods

2.1. Subjects

All subjects were right-handed. The schizophrenia group comprised 42 patients (21 men and 21 women; mean age=29.24, SD=5.58), referred to the Psychiatric Department of Kyoto University Hospital, who met the criteria for schizophrenia based on the structured clinical interview for DSM-IV Axis I Disorder-Patient Edition (SCID-P, Version 2.0). Twenty-four subjects were diagnosed as the paranoid subtype of schizophrenia, six as the disorganized subtype, one as catatonic, three as the residual subtype, one as the undifferentiated subtype, four as having schizophreniform disorder, and three as having schizoaffective disorder. All patients were receiving antipsychotic medication, and haloperidol equivalents were calculated according to Inagaki (Inagaki, 2004). All patients were physically healthy at the time of scanning and psychological tests. None had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse. The control group consisted of 24 healthy individuals (12 men and 12 women) who were matched for age and education level with the schizophrenia group. None had any history of neurological or psychiatric illness. The structural clinical interview for DSM-IV Axis I Disorder-Nonpatient Edition (SCID-NP, Version 2.0) was used to assess the presence or absence of DSM-IV Axis I disorders. Table 1 summarizes the demographic characteristics of the two groups. All subjects provided written informed consent after a complete description of the study. This study was granted approval by the Committee on Medical Ethics of Kyoto University.

2.2. MRI acquisition

All magnetic resonance imaging scans were obtained at the Kyoto University Hospital using a 3 T MR scanner (GE Medical Systems, Milwaukee). Diffusion-weighted images were acquired using a single-shot echo planar imaging (EPI) sequence in alignment with the anterior commissure–posterior commissure (AC–PC) plane. The acquisition parameters were as follows: echo time (TE), 79 ms; repetition time (TR), 5200 ms; 128×128 matrix; field of view (FOV), 220×220 mm^2 (nominal resolution 1.7188 mm); 40 continuous axial slices of 3.0 mm thickness; 12 axis motion-probing gradient, and $b$value=700 s/mm^2. To enhance the signal-to-noise (S/N) ratio, imaging was repeated four times. The acquisition time per dataset was approximately 100 s. FA was defined as the standard deviation of eigenvalues from the mean eigenvalue normalized by the square norm of eigenvalues. Parametric images of FA were calculated with a computer program (DTI-Studio, version 2.40; Johns Hopkins University, Baltimore, USA). Among the axial slices which visualize portions of a CB, the most caudal slice was discarded. This discarded image generally visualizes a middle portion of the CB. Three consecutive axial slices just inferior to that image visualize well the anterior and posterior portions of the CBs in our 3 mm thickness (no

gap) axial images. On the FA map of these three images, regions-of-interest (ROIs) for left/right anterior/posterior CBs were defined; round ROIs (diameter=4 pixels) were placed for each target region (Fig. 1). Color-coded tensor maps were simultaneously displayed with an FA-map as guidance for valid ROI placement in the CBs. In the color-coded tensor maps, pixels were characterized as either anterior-posterior (green), left-right (red), or vertical (blue) depending on the direction of the eigenvector of the diffusion tensor. In addition, to heighten the validity of ROI placement further, fiber tracking was performed from each ROI, confirming the CBs emerging from the defined ROIs (Fig. 1). DTI-Studio was also used to perform fiber tractography on the basis of fiber assignments derived by means of the continuous tracking method (Mori and van Ziji, 2002). Tracking from all of the pixels inside the brain was performed, and tracking results that penetrated the ROIs, on the basis of the known anatomic distributions of tracts, were assigned to specific tracts. The turning angle of two consecutive vectors was 75° during tracking. Propagation in each fiber tract was terminated if a voxel with an FA value of less than 0.2 was reached. For each target region, the resultant FA values in each circular ROI were averaged for three consecutive slices.

All of the FA measurements were performed by the first author (HF). To determine the reliability of the measurements, 10 subjects were randomly selected and measurements of these subjects were performed independently by two raters (HF, MS). Intrarater reliability was assessed by one (HF), and interrater reliability was assessed by two (HF, MS). Both raters were blinded to participant details, including the study group, and the results of both neuropsychological and psychopathological assessments. The intraclass correlation coefficients for the assessment of FA values in the anterior and posterior CBs were 0.92 and 0.90, respectively; the interclass correlation coefficients for the assessment of FA values in the anterior and posterior CBs were 0.91 and 0.89, respectively. This suggests that the reliability of this measure was satisfactory.

2.3. Clinical and neuropsychological assessment

Subjects were assessed when they were in a clinically stable phase. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Table 1) (Kay et al., 1987). Estimated verbal and performance IQ were obtained from subtasks of vocabulary and block design in WAIS-R, respectively, by transforming scores corrected for age into *T* scores.

2.4. Statistical analysis

All statistical analyses were carried out using SPSS version 12.0.

2.4.1. Fractional anisotropy differences between schizophrenia patients and healthy participants

The FAs in the anterior and posterior CBs were analyzed separately. Repeated measures analysis of variance (ANOVA) was applied, with group (schizophrenia patients, control subjects) as a between-subject factor and side (right, left) as a within-subject factor. In these analyses, statistical significance was set at $p<0.05$. Although significance testing helps illustrate the nature of group differences, it does not assess the degree of relationships between independent and dependent variables. Thus, we also reported partial eta-squared values ($\eta^2 p$), which are indices of effect size when using ANOVAs to analyze data. $\eta^2 p$ values range from 0 to 1 and are defined as the proportion of the total

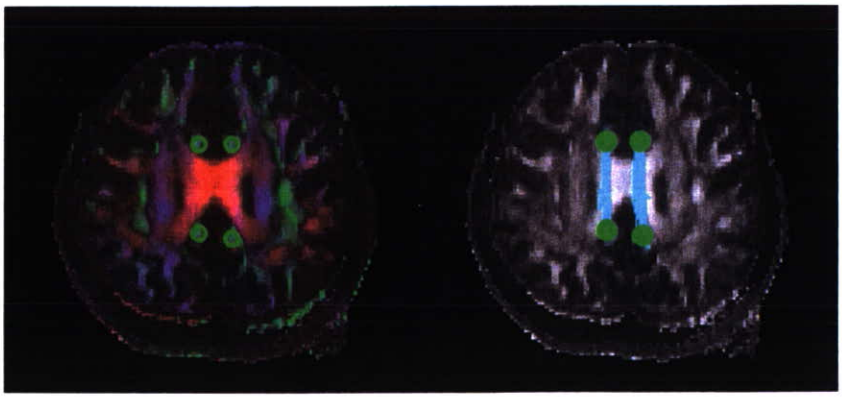

Fig. 1. Localization of anterior and posterior cingulum bundles through fractional anisotropy maps and color-code tensor images. The right-hand image shows the regions of interest and corresponding fiber tracts displayed on a fractional anisotropy map. The left-hand image is the corresponding color-coded tensor image.

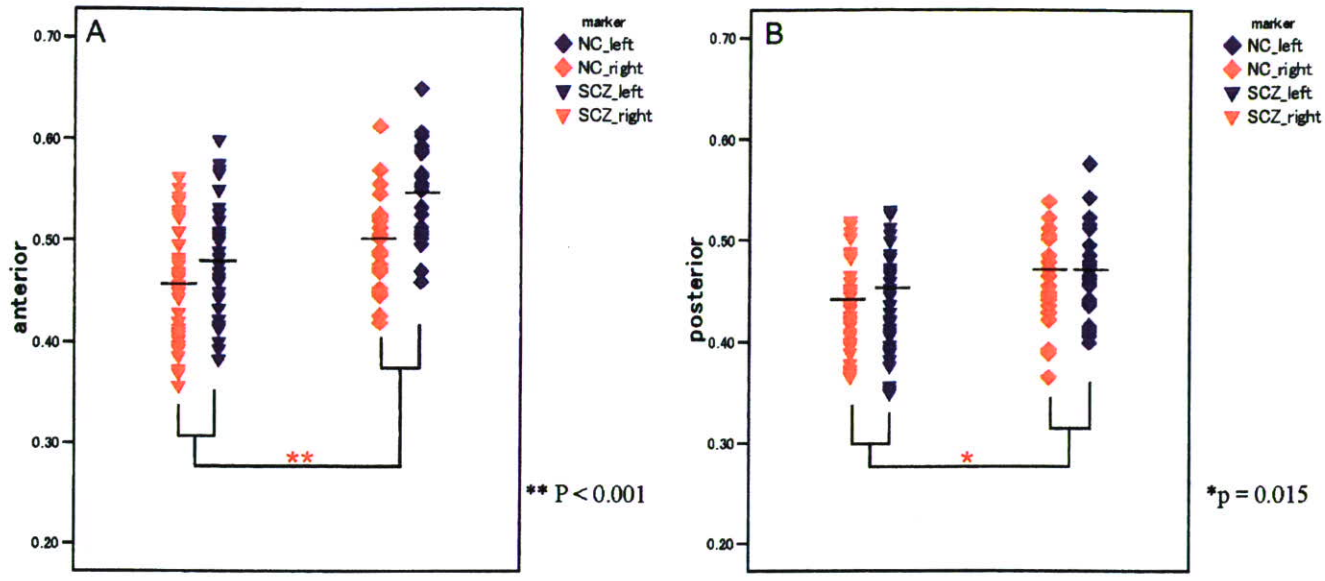

Fig. 2. A, B. Fractional anisotropy in the anterior (A) and posterior (B) cingulum bundles in normal controls and patients with schizophrenia. Abbreviations; SCZ=schizophrenia, NC=normal control.

variation attributable to the factor, partialling out other factors from the total nonerror variation (Tabachnick and Fidell, 2001).

2.4.2. Correlation analysis

After confirming the normative distribution of the data, we applied Pearson's correlation coefficient to investigate the relationship between FA values and psychopathological measures in the patient group. Furthermore, partial correlation coefficients were calculated to control for the effects of age, gender, educational attainment, illness duration and antipsychotic medication dosages. To maintain an overall alpha value of 0.05 (two-tailed), we applied Bonferroni correction to the probability values associated with the 8 correlation coefficients that we computed (i.e., correlation of the four target regions of interest with positive and negative symptom scores); consequently, we accepted any correlation coefficient

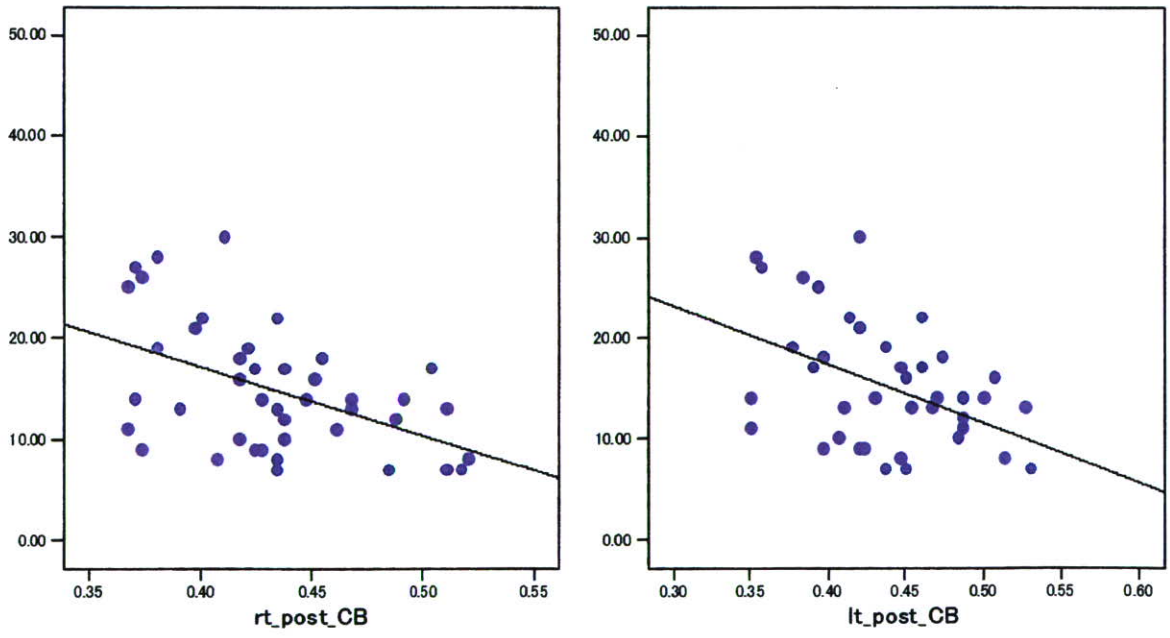

Fig. 3. Fractional anisotropy in the posterior cingulum bundle plotted against the positive symptom scores of patients with schizophrenia. Abbreviations: rt_post_CB=fractional anisotropy in the right posterior cingulum bundle; lt_post_CB=fractional anisotropy in the left posterior cingulum bundle.

Table 2
Correlations between fractional anisotropy in the cingulum and psychopathology in patients with schizophrenia

Score for correlation/ control variables	FA (right anterior)	FA (left anterior)	FA (right posterior)	FA (left posterior)
	Partial correlation (*r*)	Partial correlation (*r*)	Partial correlation (*r*)	Partial correlation (*r*)
PANSS positive symptom score	− 0.019	− 0.232	− 0.485**	− 0.467**
Age, sex, education			− 0.547**	− 0.530**
Age sex, education, illness duration			− 0.489**	− 0.499**
Age, sex, education, illness duration, medication			− 0.562**	− 0.569**
PANSS negative symptom score	0.145	0.064	− 0.042	− 0.050

Abbreviation; FA = fractional anisotropy.
** $p<0.00625$.

with an associated probability value of less than 0.00625 (0.05 divided by 8) as significant.

3. Results

3.1. Demographic data

There were no group differences in age, handedness, gender, education, and IQs (Table 1). Although all schizophrenic patients had received neuroleptic medication, no relationships were found between the diffusion measures and estimates of haloperidol equivalents ($r=0.217/0.111$, $p=0.167/0.484$, for right/left anterior CBs; $r=0.105/0.138$, $p=0.507/0.383$, for right/left posterior CBs).

3.2. Fractional anisotropy differences between schizophrenia patients and healthy participants

In the right anterior CB, mean FA values in patients and control subjects were 0.456 (SD=0.056) and 0.497 (SD=0.046), respectively; in the left anterior CB, they were 0.482 (SD=0.058) and 0.543 (SD=0.049), respectively; in the right posterior CB, they were 0.432 (SD=0.044) and 0.462 (SD=0.043), respectively; and in the left posterior CB, they were 0.441 (SD=0.050) and 0.468 (SD=0.048), respectively (Fig. 2A, B).

In the anterior CBs, repeated measures ANOVA showed a significant group effect ($F=15.116$, $df=1, 64$, $p<0.001$, $\eta^2p=0.191$), a significant laterality effect ($F=74.797$, $df=1, 64$, $p<0.001$), and a significant group-by-laterality interaction ($F=5.337$, $df=1, 64$, $p=0.024$). Although simple main effect analyses revealed that the FA values in control subjects were greater than those in schizophrenia patients on both sides ($t=-3.070$, $df=64$, $p=0.003$ for FA in the right hemisphere; $t=-4.322$, $df=64$, $p<0.001$ for FA in left hemisphere), a significant interaction indicated that the normal asymmetry (larger FA value in the left CB) was attenuated in schizophrenia patients.

In the posterior CBs, repeated measures ANOVA also showed a significant group effect ($F=6.207$, $df=1, 64$, $p=0.015$, $\eta^2p=0.088$) and a significant laterality effect ($F=4.469$, $df=1, 64$, $p=0.038$), but no group-by-laterality interaction ($F=0.064$, $df=1, 64$, $p=0.802$). FA values in control subjects were also greater than those in schizophrenia patients on both sides (right; $t=-2.602$, $df=64$, $p=0.012$, left; $t=-2.172$, $df=64$, $p=0.034$).

To compare our results with those of a study by Wang et al. (Wang et al., 2004), which is the only study to have investigated FA values in both anterior and posterior CBs in patients with schizophrenia, but only in male subjects, a supplementary analysis was applied using only data from male subjects (21 schizophrenia patients, 12 control subjects). Repeated measures ANOVA of data from anterior CBs showed a significant group effect ($F=7.936$, $df=1, 31$, $p=0.008$), a significant laterality effect ($F=32.831$, $df=1, 31$, $p<0.001$), and a trend toward a group-by-laterality interaction ($F=3.182$, $df=1, 31$, $p=0.084$). Repeated measures ANOVA of data from posterior CBs showed no significant group effect ($F=0.897$, $df=1, 31$, $p=0.351$) and a trend toward a laterality effect ($F=2.968$, $df=1, 31$, $p=0.095$), but no group-by-laterality interaction ($F=0.436$, $df=1, 31$, $p=0.514$).

As well, considering the heterogeneity of our patient populations, we re-analyzed the data excluding 7 patients (4 patients diagnosed with schizophreniform disorder and 3 patients diagnosed with schizoaffective disorder) from our initial populations. In the anterior CBs, repeated measures ANOVA showed a significant group effect ($F=14.867$, $df=1, 57$, $p<0.001$, partial eta-squared value (η^2p)=0.207), a significant laterality effect ($F=66.296$, $df=1, 57$, $p<0.001$), and a significant group-by-laterality interaction ($F=6.744$, $df=1, 57$, $p=0.012$). In the posterior CBs, repeated measures ANOVA showed a significant group effect ($F=10.190$, $df=1, 57$, $p=0.002$, $\eta^2p=0.152$) and a significant laterality effect ($F=4.046$, $df=1, 57$, $p=0.049$), but no group-by-laterality interaction ($F=0.059$, $df=1, 57$, $p=0.810$). Altogether, the re-analysis of the smaller

patient populations was essentially consistent with that of our initial analysis.

3.3. Correlation analysis

The correlations between FA values and psychopathological scores of schizophrenia patients are shown in Fig. 3. Both left and right FA values in the posterior CBs were significantly inversely correlated with positive symptom scores. This correlation remained significant when the partial correlation was calculated, controlling for age, gender, educational attainment, illness duration or neuroleptic medication dosages (Table 2). No other significant relationships between FA measures and symptom ratings were demonstrated. Additionally, we performed the same correlational analysis with 35 patients (excluding the 7 patients with schizoaffective or schizophreniform disorders). Both left and right FA values in the posterior CBs were also significantly inversely correlated with positive symptom scores ($r=-0.408$, $p=0.015$, $r=-0.385$, $p=0.022$, respectively). No other significant relationships between FA measures and symptom ratings were demonstrated. Thus, the re-analysis of the smaller patient populations ($n=35$) was essentially consistent with that of our initial analysis.

4. Discussion

Several previous studies have investigated FA values in the anterior CBs of patients with schizophrenia, and demonstrated decreased FA (Sun et al., 2003; Kubicki et al., 2003; Wang et al., 2004). Our study replicated these previous findings. Regarding posterior CBs, two recent studies applying a voxel-based approach have demonstrated a reduction in FA (Mori et al., 2007; Schlosser et al., 2007). However voxel-based approaches could potentially be contaminated with registration or normalization errors. Thus, our study is the first to demonstrate abnormal integrity of posterior CBs in schizophrenia using a direct ROI-based approach. In addition, as we performed FA measurements guided by fiber tracking, our findings could be considered the most reliable among all previous DTI studies of CBs in patients with schizophrenia, in light of the methodological advantages.

The predominant interest in the anterior CB over the posterior may be due to the fact that the adjacent anterior cingulate cortices (ACCs) has attracted considerable attention in schizophrenia research. In schizophrenia, functional and structural abnormalities of the ACCs have been reported in many neuroimaging, post-mortem and histopathological studies (Andreasen et al., 1992; Carter et al., 1997; Takahashi et al., 2002, 2003; Benes et al., 1991; Benes, 1998), and a critical role has been proposed for it in the pathophysiology of schizophrenia (Benes, 1998; Tamminga et al., 2000).

In parallel with the attention to the ACCs, pathology of the CBs underlying the ACCs has also been suspected. Cingulotomized patients with small bilateral lesions in the anterior cingulate gyrus showed deficits of attention and executive dysfunction (Benes, 1993). Cognitive dysfunction due to lesions in such domains mimics those characteristic of schizophrenia patients.

The results of previous DTI studies of anterior CBs in patients with schizophrenia have been unanimous regarding the reduced FA in this region (Sun et al., 2003, Kubicki et al., 2003, Wang et al., 2004). However, results are inconsistent regarding whether lateralized abnormality exists or not; Kubicki et al. (2003) have reported that a reduction in bilateral FA in anterior CBs is parallel, while Wang et al. (2004) have reported that normal asymmetry (left FA > right FA) of anterior CBs is diminished in patients with schizophrenia. Regarding this laterality issue, our findings suggest a lateralized abnormality of the anterior CBs in patients with schizophrenia, consistent with the report by Wang et al. (2004); that is, the normal asymmetry of FA in anterior CBs is attenuated in schizophrenia. In addition to replicating the same lateralized pattern of anterior CB abnormality in male schizophrenia subjects, our study is the first to demonstrate such a lateralized abnormality in patients with schizophrenia that is not gender specific.

Little attention has been paid to the posterior CBs, and the only study which investigated FA values in this region failed to demonstrate a reduction in FA in patients with schizophrenia (Wang et al., 2004). In our study, for the first time, bilaterally reduced FA values in posterior CBs were demonstrated in patients with schizophrenia. This discrepancy might be due to the fact that the larger sample size of our study increased the statistical power to enable us to demonstrate a group difference. However, the pattern of FA reduction was different from that in anterior CBs. First, the magnitude of FA reduction in posterior CBs (effect size of group difference of mean FA; $\eta^2 p=0.088$) was smaller than that in anterior CBs (effect size of group difference of mean FA; $\eta^2 p$ value$=0.191$). Second, bilateral FA reductions were parallel, unlike the findings of lateralized abnormality in anterior CBs. These results suggest that posterior CBs are disrupted in patients with schizophrenia, in addition to anterior CBs, and that anterior and posterior CB abnormalities are qualitatively different, possibly having a differential

pathophysiological background and a differential impact on the psychopathology of schizophrenia.

In our study, no relationships were demonstrated between FA in anterior CBs and psychopathology. A previous report has suggested that reductions in the volume of anterior cingulate WM were associated with the negative symptoms in early-onset schizophrenia (Paillere-Martinot et al., 2001). As well, Choi et al. (2005) demonstrated that a smaller volume of caudal anterior cingulate gray matter was correlated with more severe positive symptoms in schizophrenia. However, their imaging modality, sample size, and patient characteristics were different from ours. More importantly, regional FA reduction could occur independently of WM volume reduction (Agartz et al., 2001; Lim et al., 1999) or of adjacent gray matter volume reduction (Fujiwara et al., 2007) in patients with schizophrenia. Thus, reductions in FA, WM volume or gray matter volume might be associated with differential psychopathological aspects of schizophrenia. Nestor et al. have demonstrated relationships between FA reductions in anterior CBs and executive dysfunctions in patients with schizophrenia (Nestor et al., 2004). Thus, pathology of anterior CBs could be associated with specific cognitive dysfunction, rather than with the psychopathology of schizophrenia.

On the other hand, an association of FA values in posterior CBs with positive symptom scores was found in our study. Although the posterior cingulate cortex (PCC) has been less extensively investigated in imaging studies of patients with schizophrenia, a few voxel-based morphometric studies have shown gray-matter reduction in the PCCs in these patients (Sowell et al., 2000; Hulshoff Pol et al., 2001), and a recent longitudinal MRI study demonstrated posterior cingulate gray-matter loss in parallel with psychosis development (Pantelis et al., 2003). Suzuki et al. have demonstrated a reduction in the volume of the posterior cingulate gray matter and its correlation with Schneider's first rank symptoms in schizophrenic patients (Suzuki et al., 2005). Finally, several functional imaging studies have also revealed an abnormal metabolism in the posterior cingulate gyrus (Andreasen et al., 1997; Haznedar et al., 1997), and a negative correlation between cerebral blood flow in this region and Schneider's first-rank symptoms (Franck et al., 2002) in schizophrenic patients. Pathology of PCCs has been hypothesized to cause internally generated thoughts or actions to be imbued with abnormal perceptual qualities and misattributed to external agencies (Suzuki et al., 2005). Thus, considering that posterior CBs constitute the major efferent and afferent fibers to and from the PCCs, the abnormal integrity of posterior CBs together with the possible pathology of the PCCs might underlie the genesis of the positive symptoms of schizophrenia.

We should note several limitations to our study. First, all participants were right-handed. Second, the focus of this study was restricted to cingulate white matter. Finally, the associations between FA value and psychopathology were investigated in terms of a correlation analysis; thus, the relationships between abnormal integrity of the CBs and neuropsychological dysfunctions, such as executive dysfunctions or memory dysfunctions, remain unclear.

In conclusion, in our DTI study, we show a non-lateralized posterior CB abnormality in patients with schizophrenia in addition to a lateralized anterior CB abnormality. Moreover, direct relationships between posterior CB abnormality and positive symptoms were suggested. In future studies, we will aim to clarify the relationships between the abnormality of posterior CBs and specific cognitive functions. Such knowledge should provide us with valuable insights into the function of this white matter bundle.

Role of funding source

The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Fujiwara, H., Murai, T., Namiki, C., Sawamoto, N., Fukuyama, H. and Hayashi, T. designed the study and wrote the protocol. Hirao, K., Shimizu, M. and Miyata, J. managed the literature searches and analysis. Fujiwara, H. undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest.

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特集❖触法精神障害者のアセスメントと治療

医療刑務所における拘禁反応の臨床的検討

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抄録：拘禁反応は，一般的に未決拘禁下で発症し，時間経過や拘置所・刑務所での初期治療で軽快することが多い。しかし医療刑務所では，初期治療で改善しない症例が移送されてくる。当所の拘禁反応例では，拘禁の状況も拘置所とは異なり，また既決後も症状が持続しているという点で一般的な拘禁反応とは若干性質が異なる可能性がある。今回われわれは当所でみられた拘禁反応19症例において，その病態の特徴や傾向の把握のため，多変量解析の手法を用いて検討した。結果としては，拘禁神経症では，既決後に症状が持続しても治療効果が得られる傾向がみられた。また反応性妄想状態では，高齢発症で心因的要因が少ない群と考えられるのに対し，原始反応や反応性気分変調は，若年発症で心因的要因が多い群と考えられた。また反応性朦朧状態と反応性妄想状態は，疾患群として連続している可能性があることが示唆され，治療が困難である傾向がみられた。

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Key words：拘禁反応(prison reaction)，拘禁精神病(prison psychosis)

1 はじめに

法律などの強制力による，厳密な意味での拘禁により発症する反応性の症状を拘禁反応という[19]。拘禁は通常まず拘置所で行われる。突発的な社会との隔絶や裁判までの不安感が被収容者の心身に影響を及ぼすと考えられる。このため拘禁反応は拘置所で発症することが多く，病態としては一般的な心因反応から拘禁性精神病と呼ばれる重度の精神障害までを包合している[1,4,8,16]。自然消失や拘置所内での治療で改善することも多いが，症例の一部では，その精神症状が持続することもある[11,12]。

当所は，医療刑務所という立場で，拘置所や刑務所で拘禁反応を発症し，症状が改善しない症例が移送されてくる。また被収容者は刑が確定しているため，集団の一人として番号をつけられ，労働が義務づけられる。心理面では拘置所での直接的な反応とは異なる，集団生活や労働への不適応反応，将来に対する漠然とした不安が予想される。このように医療刑務所での症例では，心理面や拘禁状況が拘置所と異なり，また既決後にも症状が持続しているという性質がある。そのため治療反応性も含め，一般的な拘禁反応と若干異なる病態である可能性がある。今回われわれは，症例は19例と少ないが，当所での拘禁反応の特徴や傾向を把握し今後の治療に役立てるため，多変量解析の手法を用いて検討し，その病態に関係する要因について考察した。

The assessment of prison reaction in the medical prison
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2 対象

平成18年7月～平成19年6月までに当所に入所していた被収容者のうち拘禁反応と診断され一定期間の治療が行われた19例を対象とした。なお，平成19年6月30日における当所の被収容者は精神障害者89名，精神遅滞者68名，経理夫(健常者)57名の合計214名(収容率79.6%)であり全例男性であった。

19例のうち拘置所で発症し，当所に移入となった症例が10例，拘置所で発症したが症状が軽度であり一般刑務所へ移送されたが症状が軽快せず当所移入となった症例が6例，刑務所で発症し，当所に移入となった症例が3例であった。

拘禁反応の診断は拘置所，前刑務所で精神科医によりなされているが，当所入所後に筆者を含めた精神科医2名によりもう一度評価を行い診断した。当所での診断は主にICD-10病名を用いているが，紹介病名を残しておく場合もあり，従来病名も用いている。身分帳から得られた経歴，当所での症状，治療反応性についてまとめた(表1)。

1. 経歴

発症年齢は34.2±8.7歳，入所回数3.0±3.0回，懲役刑期39.1±30.3カ月，IQ65.2±18.1であった(数値は平均値±標準偏差)。その他主な罪名，最終学歴，家庭環境を示した。遺伝負因のある症例は1例，犯罪傾向のある家系も1例であった。また幼少時より養護施設に通所していた症例が4例みられた。

覚醒剤，有機溶剤(シンナー)，大麻などの依存性薬物の使用歴があった症例は，8例(42.1%)であった。覚醒剤，有機溶剤，大麻のすべて使用したことがある症例が2例，覚醒剤，有機溶剤使用が2例，有機溶剤のみが3例，覚醒剤のみが1例であった。

精神科通院歴のあった症例は7例(36.8%)で初回入所以前に統合失調症と診断されていた症例はなかった。

2. 当所での精神症状

当所でみられた症状を，カルテ記載や実際に診察した所見を元に示した。また，小木の分類[17]を参考に5つのタイプに分類し示した(詳細は後述する)。19例中17例においては併記病名がつけられた。

3. 治療状況および効果

治療は，薬物療法，精神療法，作業療法が行われた。作業療法では精神症状に応じて，生活センターから工場勤務までの5段階に割り振られ行われた。治療の転帰を寛解，軽快，不変の3段階で示した。

3 多変量解析の方法

1. 等質性分析について

拘禁反応の発症には，生い立ち，知能，拘禁状況などのさまざまな要因が絡んでおり，またその症状も多彩で，治療反応もさまざまである。そのため被収容者にかかわるさまざまな要因をカテゴリー変数とみなし数値化することができる等質性分析を使用した。等質性分析は，数量化Ⅲ類と同様，カテゴリカル主成分分析の変形法であるが，平面状に散布図を作成することで視覚的に傾向や類似症例の対比を行うことができる。統計解析ソフトSPSS11.5J for windows categoriesの等質性分析homogeneity analysis by means of alternating least squares(HOMALS)を用いた[7]。

19症例において，表1で示した項目のうち，①小木の分類，②治療効果，③IQ，④最終学歴，⑤発症年齢，⑥精神科通院歴，⑦依存性物質使用歴，⑧両親問題，⑨懲役刑期，⑩入所回数といった10項目を10個のカテゴリー変数とみなした。

2. 10項目のカテゴリー変数の割り当て

上述した10項目について，以下のようにカテゴリー変数を割り当てた。

【小木の分類】小木の分類から[17]，19症例を5つのタイプに診断し，5カテゴリーとした。小木によれば，拘置所での拘禁反応では，拘禁神経症，原始反応，反応性気分変調が多かったとしている[9,18]。

a) 反応性妄想状態 (n=7)

攻撃的妄想，被害的妄想，逃避的妄想を示す。虚言との区別が困難なこともある。

表1　拘禁反応19症例の特徴

	発症	入所	刑期	主な罪名	IQ	学歴	家庭環境	依存性薬物	精神科通院歴	症状	タイプ	転帰	併記病名
1	23歳	初犯	36カ月	傷害致死	83	大退	祖父を殺害	−	うつ病	憑依妄想，命令形幻聴	妄想	不変	幻覚妄想状態
2	23歳	初犯	78カ月	強盗，強姦	68	中卒	両親離婚	+	なし	解離症状，異物嚥下，幻聴，吐き気	朦朧	軽快	幻覚妄想状態，解離性障害
3	27歳	2回	24カ月	強制わいせつ	78	中卒	両親離婚	−	なし	興奮，拒薬，拒食，幻聴	原始	寛解	統合失調症の疑い
4	27歳	2回	22カ月	窃盗	37	中卒	特になし	−	なし	頭痛，不安，焦燥，徘徊	神経症	寛解	精神遅滞
5	28歳	初犯	48カ月	強盗	80	中卒	特になし	−	うつ病	亜昏迷，抑うつ，異物嚥下，幻聴	原始	軽快	躁うつ病の疑い
6	29歳	2回	36カ月	強盗	75	中卒	両親離婚	−	強迫神経症	抑うつ，異物嚥下，幻覚	変調	不変	なし
7	29歳	2回	14カ月	窃盗	60	高退	両親離婚	+	なし	攻撃性，不機嫌，頭痛，腹痛，腰痛	神経症	軽快	てんかん疑い，覚醒剤後遺症疑い
8	30歳	初犯	10カ月	器物破損	70	高退	姉が前科あり	−	なし	興奮，攻撃的妄想，独語	妄想	不変	発達障害の疑い
9	31歳	2回	24カ月	傷害	46	中卒	両親離婚	+	不眠，不安	腰痛，手足しびれ，排尿困難	神経症	不変	精神遅滞
10	31歳	初犯	10カ月	詐欺，窃盗	45	中卒	特になし	−	てんかん	解離症状，胸焼け	朦朧	不変	精神遅滞，てんかん
11	33歳	初犯	96カ月	放火未遂，詐欺	92	大退	特になし	−	なし	体感幻覚，自殺企図，妄想	妄想	軽快	なし
12	35歳	3回	108カ月	強制わいせつ致傷	64	中卒	特になし	−	なし	被害関係妄想，攻撃性	妄想	軽快	妄想性障害疑い
13	37歳	6回	24カ月	常習累犯窃盗	53	中卒	元暴走族員	+	なし	被害妄想，幻聴，幻視	妄想	不変	精神遅滞
14	37歳	2回	14カ月	窃盗	78	中卒	父自殺，遺伝負因	+	なし	頭痛，腹痛，不安，焦燥	神経症	寛解	うつ状態
15	40歳	5回	22カ月	覚醒剤取締り法違反	99	高退	特になし	+	薬物依存症	不眠，便秘	神経症	寛解	覚醒剤後遺症疑い
16	42歳	7回	24カ月	常習累犯窃盗	70	中卒	父がアル中	−	なし	幻聴，妄想	妄想	不変	精神遅滞
17	42歳	4回	72カ月	殺人未遂	37	中卒	特になし	+	なし	不眠，腰痛，便・尿失禁	神経症	軽快	精神遅滞
18	51歳	初犯	66カ月	強盗，強姦未遂	59	大卒	特になし	−	うつ状態	的はずれ応答，転換症状，幻聴	朦朧	不変	うつ状態
19	55歳	13回	14カ月	詐欺	45	中卒	両親と生き別れ	+	なし	多弁，迂遠，退行，攻撃的妄想	妄想	軽快	統合失調症疑い

b）拘禁神経症（n=6）

体に限局した痛みや違和感，疲労感，倦怠感などの不定愁訴の多いタイプ。最も頻繁に認められる。

c）反応性朦朧状態（n=3）

Ganser症候群と拘禁性ヒステリーが代表的であり，何らかの意味で意図的な傾向が前面に表出するタイプ。原始反応と詐病の中間状態と考えられている。

d）原始反応（n=2）

憤怒発作や極度の混乱など感情の爆発や昏迷を呈するタイプ。発作的に自傷行為を行うこともある。

e）反応性気分変調（n=1）

反応性うつ状態，躁状態を含む。うつ状態では，意気消沈し，面会を避け，緘黙を呈することもある。死刑囚では，反応性躁状態がみられ，笑いながら泣いたりすることもある。

【治療効果】治療効果は，軽快・不変の2カテゴリーとした。

【IQと学歴】IQは，35～50を精神遅滞，50～70を軽度遅滞，70～80を境界域，80以上を正常の4カテゴリーとした。学歴は，中卒・高校中退・高卒・大学以上(大学退学，卒業)の4カテゴリーとした。

【発症年齢】発症年齢は，20代・30代・40代以上の3カテゴリーとした。

【精神科通院歴・依存性薬物使用・両親問題】精神科通院歴は，通院・未通院を2カテゴリーとした。依存性薬物使用は，使用・未使用の2カテゴリーとした。両親問題は，あり(両親離婚，父親自殺，両親と生き別れ)・なしの2カテゴリーとした。

【懲役刑期・入所回数】懲役刑期は，1年未満・1～2年・2～3年・3年以上の4カテゴリーとした。また，入所回数は，初犯・2回・3回以上の3カテゴリーとした。

4 結果

1. オブジェクトスコアによる2つの次元へのカテゴリー負荷

各カテゴリーが2つの次元に分類された等質性分析の結果を表2に示した。すべての項目は次元1と次元2の2つの軸において，正または負のカテゴリー負荷を示している。表2においてそれぞれの軸に対して大きく負荷している主な項目を表3に示した。そして次元1をX軸，次元2をY軸とし，平面状にオブジェクトスコアをプロットし散布図を作成した(図1)。視覚的に近接あるいは対立している項目に注目した。

次元1(散布図上X軸)は，「拘禁神経症」が正，「反

表2 10項目をカテゴリー変数とした等質性分析の結果

カテゴリー変数	カテゴリー	人数	オブジェクトスコア	
			次元1	次元2
タイプ	妄想	7	−0.473	0.673
	朦朧	3	−1.033	−0.037
	原始反応	2	0.94	−1.695
	神経症	6	1.054	0.165
	気分変調	1	−0.103	−2.2
治療効果	軽快	11	0.443	0.008
	不変	8	−0.61	−0.011
IQ	正常	4	−0.712	0.114
	境界	5	0.229	−0.612
	軽度遅滞	5	−0.081	0.238
	精神遅滞	5	0.422	0.464
最終学歴	中卒	13	0.259	−0.12
	高退	3	0.454	0.416
	高卒	0	0	0
	大学以上	3	−1.578	0.102
発症年齢	20代	7	0.115	−0.987
	30代	7	−0.185	0.309
	40代以上	5	0.098	0.948
精神科通院歴	通院	7	−0.549	−0.422
	未通院	12	0.32	0.246
依存性薬物	使用	8	0.766	0.392
	未使用	11	−0.557	−0.285
両親問題	あり	7	0.544	−1.037
	なし	12	−0.317	0.605
懲役刑期	1年未満	2	−1.091	0.353
	1～2年	5	1.113	0.349
	2～3年	4	0.4	−0.72
	3年以上	8	−0.623	0.27
入所回数	初犯	7	−1.082	−0.169
	2回	6	0.915	−0.866
	3回以上	6	0.348	1.063