recognition deficits in schizophrenia in the context of social cognition (Lee et al., 2004). One of the main questions is whether schizophrenia patients have specific impairments in facial emotion recognition. Consistent findings show that they experience difficulty in the perception of negative emotional displays when compared with that of positive emotional displays (Edwards et al., 2002). However, there is a lack of consistency among reports regarding the category of negative emotions that cannot be recognized by schizophrenia patients. The majority of studies reported that the greatest difficulty was in recognizing fear (Mandal et al., 1998; Edwards et al., 2002); however, some reported impairment in recognizing negative emotions other than fear (Bediou et al., 2005).

1.2. Neural basis of facial emotion recognition deficits in schizophrenia

The neural system implicated in facial emotion recognition has been proposed to include the amygdala, the fusiform gyrus and the superior temporal sulcus (Adolphs, 2002). In particular, the amygdala is suggested to be closely involved in the recognition of negative facial emotions, and this theory has been supported by both lesion studies and imaging studies. Human lesion studies have consistently found impaired recognition of facial emotion following bilateral amygdala damage; this impaired recognition is often disproportionately prominent for fear (Adolphs et al., 1994, 1995; Phillips et al., 1998; Calder et al., 2001), but sometimes encompasses multiple negative emotions including fear, anger, disgust, and sadness (Scott et al., 1997; Schmolck and Squire, 2001). Functional magnetic resonance imaging (fMRI) studies have also reported that the amygdala is activated in a disproportionately greater fashion by negative facial emotions (Phillips et al., 1998; Whalen et al., 2001).

Meanwhile, a number of morphometric MRI studies on schizophrenia demonstrated abnormalities in various cortical and subcortical structures (Shenton et al., 2001), including the areas that are considered to be involved in emotional processing as described above. The amygdala has thus been measured in several morphometric studies in schizophrenia. However, the results of these studies are not consistent. Some studies indicated that amygdalae of schizophrenia patients were smaller bilaterally than those of normal controls (Joyal et al., 2003; Niu et al., 2004), although one study showed right-unilateral amygdalar volume reduction in schizophrenia (Pearlson et al., 1997). There were also several studies with more complex results. Gur et al. (2000), for example, reported that only men with schizophrenia had smaller amygdalar volume, while Kalus et al. (2005) found volume reduction only in raw volumes, but not in adjusted volumes. Contrary to this, other studies showed no difference in amygdalar volume between schizophrenia subjects and normal controls (Altshuler et al., 2000; Niemann et al., 2000; Staal et al., 2000; Szeszko et al., 2003). More recently, studies of comparatively larger populations have also reported no difference (Tanskanen et al., 2005; Velakoulis et al., 2006), and neither did a recent meta-analysis study (Vita et al., 2006).

1.3. Aim of the present study

Thus both structural abnormalities of the amygdala and impaired facial emotion recognition have been reported in schizophrenia. Therefore, these morphological abnormalities may underlie dysfunction in facial emotion recognition in schizophrenia. However, the relationship between the two has not been directly investigated to any substantial extent. To our knowledge, only one study has examined the relationship between an emotional task and amygdalar volume (Exner et al., 2004). This study suggested that amygdalar volume reduction was related to emotional processing deficits in schizophrenia. However, this study employed an emotional memory task, which investigated learning abilities elicited by facial expression, but not facial recognition ability itself. Hence, we performed both volumetric analysis of the amygdala and evaluation of facial emotion recognition performance in the same subjects.

As described earlier, schizophrenia patients were reported to have smaller amygdalar volumes than normal controls; however, this finding was not completely uniform. This inconsistency may have resulted from methodological differences including patient sampling, MRI protocols, and volumetric procedures for measuring the amygdala. In particular, small brain structures such as the amygdala need to be delineated by MRI, which allows three-dimensional volume acquisition with high spatial resolution (Niu et al., 2004). In the present study, therefore, we used a 3.0-Tesla MRI machine that provides images with a higher resolution and a better three-dimensional orientation than those seen in previous studies.

For the facial emotion recognition task, we used a task of recognizing the intensity of basic emotions in facial expressions (Adolphs et al., 1994). This task was originally developed for brain-damaged patients to test their facial affect recognition abilities (Adolphs et al., 1994, 1999), and it has been clearly demonstrated that patients with bilateral amygdala damage were significantly impaired in recognizing fearful, but not happy,

facial expressions. In addition, this task has been considered to minimize floor and ceiling effects, which may help overcome the methodological shortcomings often observed in emotion-labeling tasks (Edwards et al., 2002).

The present study was designed to test the following hypotheses: (1) amygdala volumes are smaller in schizophrenia subjects than in normal controls when assessed using 3T high-resolution volumetry. (2) Schizophrenia patients show specific facial emotion recognition deficits in the emotion intensity recognition task. In the event that the two above mentioned hypotheses were true, we aimed to determine the relationship between the reduced amygdalar volumes of the schizophrenia subjects and their performance in each of the disturbed emotion categories of the emotion intensity recognition task.

2. Methods

2.1. Schizophrenia subjects

The sample group comprised 20 schizophrenia patients (10 males and 10 females). These patients were inpatients and outpatients from the Department of Psychiatry, Kyoto University Hospital. Based on the *Structured Clinical Interview for DSM-IV* (*SCID*), each patient fulfilled the DSM-IV criteria for schizophrenia or a schizoaffective disorder. Eleven subjects suffered from the paranoid subtype of schizophrenia; five, from the disorganized subtype; and two, from the catatonic subtype. Additionally, two subjects were diagnosed with schizophreniform disorder. None had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse. All patients were receiving antipsychotic medication (three patients were on typical agents, 16 on atypical agents and one on both). They did not have any first degree relatives who had had psychotic episodes. Haloperidol equivalents were calculated according to Inagaki et al. (2004). Handedness was assessed by the Edinburgh Laterality Inventory (Oldfield, 1971) (Table 1).

2.1.1. Healthy controls

Schizophrenia subjects were compared with 20 matched healthy control subjects recruited from the local community. These subjects were also evaluated with the SCID. The subjects were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorders. They did not have any first degree relatives who had had psychotic episodes. The control subjects were paid for their participation and matched with schizophrenia subjects in terms of age, sex, and years of education. Handedness was also assessed by the Edinburgh Laterality Inventory (Table 1).

After a complete description of the study was given to the subjects, written informed consent was obtained. This study was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine.

2.2. Clinical and neuropsychological assessment

The subjects were assessed when they were in a clinically stable phase. Psychopathology was assessed

Table 1
Demographic, clinical and neuropsychological characteristics of subjects

	Schizophrenia (n=20)		Healthy controls (n=20)		Analysis	
	Mean	S.D.	Mean	S.D.	t (df=38)	P
Age (years)	38.8	7.2	39.1	7.1	0.13	P>0.05
Sex (male/female)	10/10		10/10		–	–
Handedness (right/left)	19/1		19/1		–	–
Education (years)	13.5	2.0	14.4	1.9	0.15	P>0.05
Age at onset (years)	27.4	6.4	–	–	–	–
Duration of illness (years)	11.6	8.7	–	–	–	–
Drug (mg/day, haloperidol equivalent)	11.9	8.9	–	–	–	–
PANSS Total	64.5	19.8	–	–	–	–
PANSS Positive	16.4	6.7	–	–	–	–
PANSS Negative	15.7	6.5	–	–	–	–
PANSS General	32.4	10.1	–	–	–	–
VIQ	97.8	16.0	107.5	14.8	1.998	P>0.05
PIQ[a]	97.8	14.9	107.0	12.7	2.11	P=0.04
BFRT	45.5	6.03	47.2	4.0	1.02	P>0.05

[a] The results of subjects with schizophrenia in the block test were significantly worse than those of healthy controls.

using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Intellegence was assessed using the vocabulary and block design subtests of the Japanese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1990; Booker and Cyr, 1986). The raw scores were corrected for age and transformed into T scores. The Benton Facial Recognition Test (BFRT) (Benton et al., 1983) was applied to assess basic visuoperceptual ability in response to facial stimuli. In this test, subjects were asked to match the faces representing the same individual, among six people who were shown with varying views and light conditions.

2.3. MRI acquisition and analysis

All subjects received an MRI scan using a 3.0-T Siemens Trio machine. The scanning parameters of the three-dimensional-magnetization-prepared rapid-gradient echo (3D-MPRAGE) sequences were as follows: echo time (TE)=4.38 ms; repetition time (TR)=2000 ms; inversion time (TI)=990 ms; field of view (FOV)=256; slice plane=axial; slice thickness=1 mm; resolution=0.94×0.94×1.0; and slice number=208. In order to increase the signal/noise ratio, we scanned all subjects three times and created average images from these three images by using statistical parametric mapping 2 (SPM2) (http://www.fil.ion.ucl.ac.uk/spm). The averaged images were displayed and measured using MRIcro software (University of Nottingham, Nottingham, UK). This software enabled us to trace objects in three directions, i.e., the sagittal, coronal and horizontal. Tracing of the amygdala was performed manually by a single rater (C.N.) blind to the diagnosis and to the results of the neuropsychological tests.

Estimates of the global gray and white matter volumes and cerebrospinal fluid (CSF) volume were obtained after an automatic brain segmentation procedure carried out by SPM2. The total intracranial volumes were the sums of the volumes of gray and white matter and CSF.

The amygdala was disarticulated from the surrounding tissue by means of manual tracing according to a standardized protocol (Pruessner et al., 2000). We referred to Watson et al. (1992) for an anatomical atlas. The boundaries of the amygdala were as follows: posterior, the appearance of gray matter superior to the aleveus and lateral to the hippocampus; superior-lateral, the thin strip of white matter that separates the amygdala from the ventral putamen; inferomedially, the intrarhinal sulcus, or the tentorial indentation separating the amygdala from the entorhinal cortex; inferolaterally, the temporal horn of the lateral ventricle which separates the amygdala from adjacent structures; and the anterior border of the amygdala was defined as being at the level of the closure of the lateral sulcus.

For estimating the intrarater reliability of the amygdala measurements, five randomly selected cases were re-assessed. Further, to assess the validity of defining the region of interest (ROI) of the amygdala and to avoid the arbitrariness of a single rater, interrater reliability was also calculated. Five randomly selected cases were analyzed using three individual raters (C.N., K.H., and M.Y.) who were blind to the diagnoses of subjects and the results of the psychological tests. The reliability of this measurement was found to be satisfactory, with an intrarater reliability of 0.99 and an interrater reliability of 0.97.

2.4. Facial emotion recognition task

The experimental procedure was identical to that of Adolphs et al. (1994). A total of 39 face stimuli — six faces expressing each of the emotions of happiness, sadness, fear, anger, disgust, and surprise and three neutral faces—were selected from the Pictures of Facial Affect series (Ekman and Freisen, 1976). In one block, the set of 39 stimuli was presented randomly with no time limit. This was repeated six times in separate blocks. For each block, one of the six emotion terms was presented, and the patients or control subjects had to evaluate the intensity of a given emotion in the facial expression on a scale of 0 (not intense at all) to 5 (very intense). After rating the stimuli involving one emotion of the six, the subjects were asked to rate other emotion terms in subsequent blocks. Thus, for each facial stimulus, the subjects rated the intensity of all six basic emotions. The patients' performance in facial emotion recognition was measured in terms of Pearson correlation scores. First, the rating profile given to each face by each patient was correlated with the mean rating profile given to that face by the group of healthy subjects ($n=20$). In the case of normal individuals, correlation coefficients were calculated between each normal individual and the remaining 19 control subjects. Thus, correlations close to 1 indicate that the subject rated the stimulus normally; correlations close to 0 (or negative) indicate that the subject did not rate the stimulus correctly. Second, to calculate the average for correlation over several faces (e.g., the average correlation for all six happy faces), a patient's correlation for each face was Fisher's Z-transformed. The Z-transformed correlations were averaged over six faces that expressed a given emotion, and the average was then inverse Z-transformed to obtain the mean correlation for that emotion (Adolphs et al., 1994, 1999). The Fisher Z-transformed scores of

Table 2
Amygdalar volumes in the subjects with schizophrenia and healthy controls

	Subjects with schizophrenia (n=20)		Healthy controls (n=20)	
	Mean	S.D.	Mean	S.D.
Intracranial volume (mm^3)[a]	1.88×10^6	2.06×10^5	1.79×10^6	2.60×10^5
Right amygdala (mm^3)[b]	1104.81	126.90	1208.94	75.12
Left amygdala (mm^3)[b]	1095.00	113.63	1181.46	73.97

[a] Intracranial volume was compared by t-test, showing there was no significant difference between the subjects with schizophrenia and healthy controls (t (38)=1.28; P>0.05).

[b] The amygdalar volume was compared in an omnibus (2) group × (2) hemisphere ANCOVA model with intracranial volume as a covariate. A significant effect of group was obtained (F(1)=10.8; P=0.002), indicating smaller amygdalar volumes in the schizophrenia group. The group × hemisphere interaction was not significant (F(1)=1.52; P>0.05). The follow-up regional one-way ANCOVA with intracranial volume as a covariate showed significant differences in both right and left amygdalar volumes between schizophrenia subjects and healthy controls (F(1, 37)=16.7; P<0.001; F(1, 37)=14.3; P=0.001, respectively).

the correlation were used in all parametric statistical analyses.

2.5. Statistical analysis

Two-tailed t-tests were applied to compare differences between groups on demographic and clinical variables. For the volumetric analysis, an overall two-factor group × hemisphere repeated measures analysis of covariance design (ANCOVA), adjusting for the intracranial brain volume, was used as an omnibus statistic. The omnibus ANCOVA model was followed up by a separate one-way ANCOVA (for adjusting the intracranial brain volume) for the left and right hemispheres. Group performances on the facial emotion recognition task were compared by an overall two-factor group × emotion repeated measures analysis of variance (ANOVA) and followed up by a post-hoc analysis with Bonferroni correction for each emotion.

Correlational analyses were used to examine the relationship between the Z-transformed scores of the facial emotion recognition task and the amygdalar volumes. Further, we also examined the relationships between the Z-transformed scores of the task and the clinical variables and between the amygdalar volumes and the clinical variables.

All analyses were two-tailed, and the alpha level was set at P<0.05. All statistical comparisons were performed using the Statistical Package for the Social Sciences (SPSS for Windows, Version 11.0).

3. Results

3.1. Neuropsychological tests

There were no significant differences in the results of the BFRT or the vocabulary subtest of the WAIS-R between the healthy controls and the schizophrenia subjects. The results in the block design subtest of the WAIS-R were slightly worse in the schizophrenia subjects than in the healthy controls (Table 1).

3.2. Volumetry of the amygdala

The intracranial volumes were compared by t-test; this test showed that there was no significant difference between the schizophrenia subjects and healthy controls (t(38)=1.28; P>0.05). The amygdalar volume was compared in an omnibus (2) group × (2) hemisphere ANCOVA model with the intracranial volume as a covariate. A significant effect of group was obtained (F(1)=10.8, P=0.002), indicating smaller amygdalar volumes of the schizophrenia subjects relative to the control subjects. The group × hemisphere interaction was not significant (F(1)=1.52, P>0.05). The follow-up regional one-way ANCOVA model with the intracranial volume as a covariate showed significant differences in both right and left amygdalar volumes between the schizophrenia subjects and healthy controls (F(1;37)=16.7; P<0.001 and F(1;37)=14.3; P<0.01, respectively) (Table 2, Fig. 1).

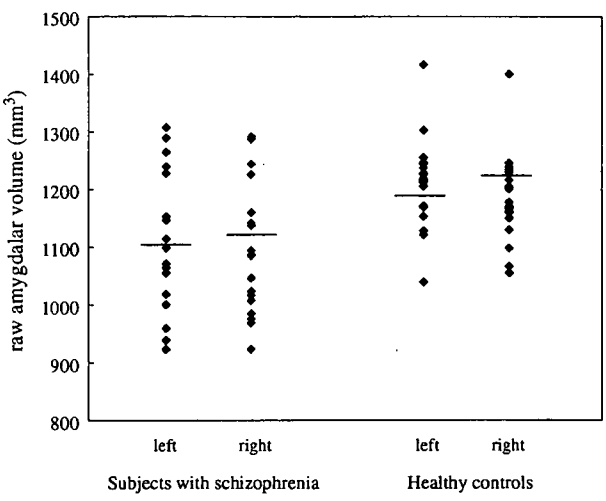

Fig. 1. Scatterplot of left and right amygdalar volume (mm^3) for schizophrenia subjects and healthy controls; group means are indicated by horizontal lines.

Table 3
Z-transformed scores of the subjects with schizophrenia and of the healthy controls

	Subjects with schizophrenia (n=20)		Healthy controls (n=20)		Analysis
	Z-transformed scores	S.D.	Z-transformed scores	S.D.	P
Happiness	3.14	1.23	3.63	0.75	P=0.13
Surprise	1.05	0.55	1.63	0.44	P<0.001*
Fear	0.90	0.36	0.98	0.30	P=0.48
Anger	0.79	0.48	1.28	0.42	P<0.001*
Disgust	0.82	0.58	1.42	0.42	P<0.001*
Sadness	0.91	0.52	1.44	0.49	P=0.001*

We carried out a (2) group × (6) emotion ANOVA with subject groups as a between-subjects factor and the basic emotion expressed by the stimuli as a within-subjects factor by using the Z-transformed correlation scores as the dependent variable. There was a highly significant effect of the type of emotion (F(5)=177.3; P<0.001) and a significant group effect (F(1)=11.7; P=0.02). There was no significant interaction between emotion type and subject group (F(5)=1.92; P>0.05).

* Post-hoc analysis using the Bonferroni correction for each type of emotion revealed that the recognition of anger, disgust, surprise, and sadness was significantly worse in schizophrenia patients than in healthy controls.

3.3. Facial emotion recognition task

We carried out a (2) group × (6) emotion ANOVA, with subject groups as a between-subjects factor and the basic emotion expressed by the stimuli as a within-subjects factor by using the Z-transformed correlation scores as the dependent variable. There was a highly significant effect of the type of emotion (F(5)=177.3; P<0.001) and a significant group effect (F(1)=11.7; P=0.02). There was no significant interaction between emotion type and subject group (F(5)=1.92; P>0.05) (Table 3). In this ANOVA, the post-hoc pair-wise comparison analyses with Bonferroni correction revealed that the differences between the scores of happiness and the other five emotions, and the scores of surprise relative to those of fear and anger, were significant (they were all P<0.01). As we found no significant relationship between emotion type and subject group, it was suggested that the schizophrenia subjects generally performed poorly in this task. However, each type of emotion provides different evidence regarding a relationship with amygdalar function. Thus, planned group comparisons for each emotion type were also performed. The results showed that the schizophrenia subjects performed significantly worse in recognizing anger, disgust, surprise, and sadness than the controls. On the other hand, the ability to recognize fear and happiness did not differ between the two groups (Table 3). Finally, as there was a significant between-group difference in PIQ, we performed an ANCOVA using PIQ as a covariate to confirm the group effect. Again, the results showed that there was a significant group effect (F(1;37)=6.4, P=0.02), together with group differences in surprise (F(1;37)=8.2, P=0.007), anger (F(1;37)=7.5, P=0.01), disgust (F(1; 37)=9.6, P=0.004) and sadness (F(1; 37)=7.3, P=0.01), revealed by one-way ANCOVA using PIQ as a covariate.

3.4. Correlation between amygdalar volume reduction and facial emotion recognition performance

We next tried to investigate correlations between the amygdalar volumes and the Z-transformed scores of the emotion recognition task. We first confirmed that the distributions of both the right and left amygdalar volumes were normal by using the Kolmogorov–Smimov test. We then conducted Pearson's correlational analyses between the amygdalar volumes and the scores of the emotions.

In the first analysis, we investigated the correlations between the total scores of all the emotions and the right and left amygdalar volumes of the schizophrenia subjects. The results showed that there were no correlations between them (between the right amygdalar volume and the summed Z-score; r=0.35, P>0.05: between the left volume and the summed Z-score; r=0.43, P>0.05). Subsequently, we moved on to the analysis of each of the emotions.

The amygdala is thought to be involved in negative facial expressions; however, we could not find any

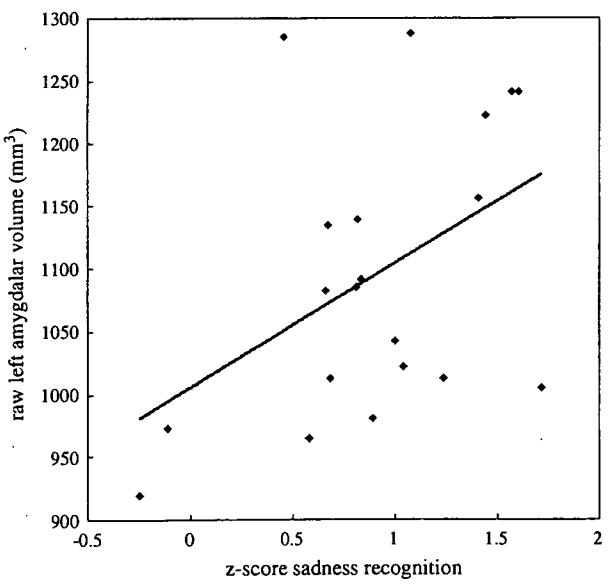

Fig. 2. Scatterplot of amygdalar volumes versus the Z-score of sadness recognition in the schizophrenia subjects. Pearson correlation analysis showed significant correlation between the score of sadness recognition and the left amygdalar volume (r=0.45; P=0.045).

difference in the ability to recognize fear among subjects showing different amygdalar volumes. We next investigated the possible correlations between the amygdalar volumes and the ability to recognize anger, disgust, and sadness, for which a group difference in emotion recognition performance had been confirmed in the above analysis. The score of the recognition of sadness correlated significantly with left amygdalar volume ($r=0.45, P=0.045$) (Fig. 2). However, the other two scores correlated with neither the right nor the left amygdalar volumes.

In addition, we investigated possible correlations between amygdalar volumes and all six scores of emotion recognition, in both the schizophrenia subjects and healthy subjects, although these analyses were outside the focus of our initial hypothesis. Significant correlations were found between the score of happiness and both the right and left amygdalar volumes in schizophrenia subjects ($r=0.49$; $P=0.029$ and $r=0.59$; $P=0.006$, respectively). Although the intracranial volumes did not correlate significantly with any scores of emotions in either the schizophrenia subjects or the healthy controls, we also investigated partial correlations with the same measures using the intracranial volumes as a covariate. The above-demonstrated relationship between the recognition of sadness and the left amygdalar volume turned out to be non-significant, but there remained a trend ($r=0.40$; $P=0.09$). All the other results remained as before.

3.5. Influence of psychopathology and antipsychotic medication

The scores of the schizophrenia patients in the recognition of any of the emotions did not correlate significantly with any psychopathological measures (PANSS Positive, PANSS Negative, and PANSS General), antipsychotic dosage, or the duration of illness. The amygdalar volumes did not correlate significantly with any psychological measures, antipsychotic dosage or illness duration (they were all $P>0.05$; see the P values in Table 4).

Table 4
Influence of psychopathology, illness duration and antipsychotic medication on the scores of the performances of the emotions and the amygdalar volumes: the P values of the correlations

	PANSS Positive	PANSS Negative	PANSS General	Illness duration	Antipsychotic dosage
Happiness	0.27	0.68	0.67	0.98	0.46
Surprise	0.45	0.45	0.68	0.16	0.52
Fear	0.51	0.36	0.67	0.32	0.23
Anger	0.50	0.96	0.71	0.23	0.72
Disgust	0.21	0.61	0.82	0.27	0.65
Sadness	0.43	0.82	0.79	0.37	0.75
Right amygdalar volume	0.50	0.18	0.11	0.23	0.72
Left amygdalar volume	0.18	0.73	0.41	0.16	0.28

4. Discussion

Three main findings emerged from this study: (1) the schizophrenia patients had smaller amygdalar volumes than the healthy controls; (2) the patients showed impairment in recognizing facial emotions, specifically anger, surprise, disgust, and sadness; and (3) the left amygdalar volume reduction in these patients was associated with impaired recognition of sadness in facial expressions.

4.1. Amygdalar volume in schizophrenia

The results of previous studies that compared the amygdalar volumes between healthy controls and schizophrenia patients have not been uniform. This inconsistency reflect the different MRI protocols applied in these studies. Since the amygdala is a relatively small structure, it is difficult to delineate the amygdala in low resolution MR images, especially to separate the amygdala from the hippocampus. Most of the previous studies used slices thicker than 1 mm (Altshuler et al., 2000; Niemann et al., 2000; Staal et al., 2000; Szeszko et al., 2003; Tanskanen et al., 2005; Velakoulis et al., 2006). In contrast, recent studies using high-resolution images with a slice thickness less than 1 mm have found amygdalar volume reductions in schizophrenia patients, although the results were not completely consistent (Gur et al., 2000; Niu et al., 2004; Kalus et al., 2005). In this study, we first used a 3.0-Tesla MRI machine that provided high-resolution images and confirmed the amygdalar volume reduction in schizophrenia.

As described in the Section 1, the discrepancy may arise from the differences between the schizophrenia subject groups in those studies. Brain structural volumes are influenced by age of onset, duration of illness (DeLisi, 1999) and neuroleptic medication (Scherk and Falkai, 2006). The discrepancy in the volumetric studies of the amygdala may reflect those factors in the subjects. In particular, recent volumetric studies have found that there is no amygdalar volume reduction in first episode schizophrenia (Velakoulis et al., 2006; Vita et al., 2006). In the present study, the schizophrenia subjects were chronic, and this may be a possible cause of the

discrepancy between our study and other studies, which mainly examined first episode schizophrenia patients.

As a method with the ability to survey the whole brain and with reduced operator bias, Voxel-Based Morphometry (VBM) has been applied to schizophrenia, and several studies have demonstrated morphological abnormality in the limbic region, including the left amygdala, left hippocampus and left parahippocampus (Honea et al., 2005). However, a comparative study has demonstrated that manual ROI tracing is superior to VBM especially for the small, topographically-complex anatomical regions (Tisserand et al., 2002). Hence, care should be taken in interpreting VBM findings for small and complex regions such as the amygdala, at least for the present.

4.2. Facial emotion recognition in schizophrenia

It is often difficult to determine whether poor facial affect recognition in reported studies on schizophrenia is due to a general deficit in face perception or due to a specific deficit in the recognition of facial emotions (Lazarus, 1984). In this study, there was no difference between the schizophrenia patients and the controls with regard to their performance in the BFRT. Our study revealed that poor performance in the facial emotion recognition task was due to a specific deficit in the recognition of facial expressions of emotions.

In addition to the finding that the patients showed general emotion recognition deficits, our planned comparison revealed that the patients performed poorly, especially for the emotions of surprise, disgust, sadness, and anger (Table 3). Our finding for happiness recognition performance was consistent with those of previous reports (Mandal et al., 1998; Edwards et al., 2002). Thus, the current data support the hypothesis of an emotion-specific deficit in the ability to recognize facial emotions and greater vulnerability to impaired negative emotion processing in schizophrenia patients.

Interestingly, we could not find any difference in the fear recognition performance between the schizophrenia subjects and the controls; this was inconsistent with the majority of previous studies (Gaebel and Wölwer, 1992; Archer et al., 1994; Edwards et al., 2002).

One possible reason for this inconsistency could be a methodological one. Most of the previous studies on facial emotion recognition in schizophrenia used labeling tasks in which subjects are requested to choose the label best describing the facial emotion stimuli presented. In the labeling task, the difficulties in recognizing each facial emotion are not always matched. Fear, in particular, is the emotion most difficult to recognize, even by healthy people (Gosselin et al., 1995). Therefore, the recognition of fear in facial expressions by schizophrenia patients in the labeling tasks, when compared with the recognition of other emotions, could be further worsened due to general cognitive impairment in schizophrenia. This could have resulted in the apparent specific impairment in the recognition of fear in the previous studies. Although such floor and ceiling effects were minimized in this emotional intensity task, it is possible that floor and ceiling effects may have blurred the group differences for happiness and fear recognition. To solve this problem, we need more rigorous matching across emotional categories, and a novel emotion task should be devised.

More importantly, the present finding with respect to recognizing fear appeared to be inconsistent with studies on amygdala-damaged patients. This may result from a possible difference in amygdalar pathology unique to schizophrenia. First, in most of the reported cases of brain-damaged patients, the amygdalae were completely and bilaterally damaged. However, the reduction in the amygdalar volume is partial in schizophrenia patients. In addition, the postmortem study of a schizophrenia patient showed a specific elevated dopamine concentration in the left amygdala (Reynolds, 1983). Further, one diffusion tensor imaging study demonstrated a significant reduction of anisotropy in the amygdalae of schizophrenia patients (Kalus et al., 2005). These various pathological possibilities could cause the different profile of the impairment between schizophrenia patients and patients with completely damaged amygdalae.

4.3. Neuromorphological correlates of facial emotion recognition in schizophrenia

The association between the recognition of sad facial emotion and amygdala function was corroborated by previous lesion studies and functional imaging studies (Sprengelmeyer et al., 1999; Blair et al., 1999; Killgore and Yurgelun-Todd, 2004). Regarding the laterality, this study showed that the sadness recognition performance in schizophrenia correlated only with the left amygdalar volume (Fig. 2). Baas et al. (2004) reported that the left amygdala was more often activated than the right amygdala in emotional tasks in general. In conjunction with this, Gläscher and Adolphs (2003) proposed that an emotionally arousing stimulus first activates the right amygdala which mediates a relatively general emotional reaction, and then the left amygdala is involved in a more specific, sustained emotional reaction. The task used in this study appears to require a detailed observation to rate facial emotions; this could explain our finding of the correlation between the left amygdalar volume

reduction and poor performance in the facial recognition of sadness.

One concern is whether, and how, we should adjust the amygdalar volume. We first used the raw amygdalar volumes for the correlation analyses and next calculated the partial correlations using intracranial volume as a covariate. It is still controversial as to how brain regions should be properly adjusted (Niemann et al., 2000). An early report by Arndt et al. (1991) had shown that head-size correlation based on proportion, ratio, or residual regression scores was less reliable than the uncorrected raw measures. One study reported that, especially in the amygdala, volume reduction in schizophrenia was found only for raw volumes, but not for adjusted volumes (Kalus et al., 2005). Small brain areas such as the amygdala could be assumed to be highly labile for methods of correlation. In the present study, we showed a significant correlation for the raw volume, but only found a trend toward a significant correlation in the partial correlation analyses. Thus, our results for a specific association between sadness recognition and left amygdalar volume in schizophrenia should be considered preliminary, and future studies of larger populations will be necessary.

5. Conclusion

In schizophrenia patients, facial emotion processing deficits are emotion-specific (sadness, surprise, disgust, and anger). Moreover, there was a reduction in both left and right amygdalar volumes. Although most studies on the functions of the amygdala have focused on the recognition of fear in facial expressions, the present study demonstrated a correlation between the left amygdalar volume and the recognition of sadness in facial expressions. It demonstrated that amygdalar dysfunction may contribute to impaired facial emotion recognition in schizophrenia.

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特集

サイコパス：情動の病そして扁桃体機能不全仮説

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Key Words
psychopath, emotion, amygdala, prefrontal cortex

1 はじめに

側頭葉内側部に左右対称に位置するアーモンド形の構造物である扁桃体は，Joseph LeDoux[28]が称した「情動脳（the emotional brain）」ということばにもみられるように，ヒトの情動を形成する神経回路の中で，最も重要な役割を果たす領域として知られている。一方で，サイコパスの病態の根底が，情動の障害であるとの指摘が数多くなされている。サイコパスでは，脅威刺激への反応が低下し[29]，情動学習に障害があり[31]，共感能力が欠如[6]している。これらのことから，必然的に，サイコパスと扁桃体との関連が想像される。

サイコパスとは扁桃体の障害なのか？

この疑問に答えるためには，まず，サイコパスという診断を理解し，サイコパスの示す障害を整理することから始める必要がある。

2 サイコパスと反社会性人格障害

反社会性人格障害（ASPD）あるいは行為障害（CD）という用語を本稿では用いなかった。DSMにおけるASPD（同様にCD）の診断基準は，犯罪的行動の記述を中心としていて，病的因子を見つけ出すにはあまりに粗雑だからである。刑務所に収容されている人々のうち70～100％がASPDの診断基準を満たしたが，サイコパスは28％にすぎなかったとの報告がある[40]。

今日，欧米を中心に議論されているサイコパスの診断基準はHare[22]のPCL-R（Psychopathy Checklist-Revised）に基づいており，従来のものとは異なっていることには注意が必要である（サイコパス概念の変遷については福井ら[21]参照）。1つだけ付記すると，Schneiderのpsychopathischen Persönlichkeiten（精神病質人格），すなわち「自らが悩むか，他者を著しく悩ませる人達」と定義されたものは，現在においては広くpersonality disorder（人格障害）全般を意味するとされている[25]。

PCL-Rによってなされるサイコパスの概念は，情動の浅薄さ，表面的な魅力，他者への共感能力の欠如といった情動的対人関係的側面（factor 1）と，非行，犯罪，攻撃性といった問題行動的側面（factor 2）の2つに大別されてい

Psychopath: emotional impairments and implications of amygdala dysfunction

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る[22]。情動的対人関係的側面(factor 1)が基準に加わることによって，情動障害の評価が可能となり，サイコパス概念はより洗練されたものになった。ASPDやCDのような雑多なものではなく，特異的な障害を共有する集団を同定することを可能にした。

事実，累犯の確率においては，サイコパスは有意にASPDを上回っている[23]。また，前向き研究によると，サイコパスとそうでない者とを比較した場合，高率にサイコパスに再犯が起こる[24]。このように，危険予測という観点からもサイコパス概念の有用性が指摘されている。一方では，サイコパスは犯罪的行動を示す人々に限定されない概念であるため，社会に適応的で成功することさえあることも指摘されている[15]。金銭や性的交渉，地位などの獲得のためには巧妙な行動を取り得ることが知られている。

以下，本稿では，Hareのいうところのサイコパスに議論を絞ることとする。

3 反応的攻撃と道具的攻撃

サイコパスの病態を考えるうえで，従来用いられている，反応的および道具的攻撃という分類を元に考えることが有効である[8]。反応的攻撃とは，感情的ないし衝動的な形を取る攻撃を指す。嫌な体験などを引き金にして，直接的に攻撃となって現れる。そこには，何ら隠された目的などは存在しない。対照的に，道具的攻撃は，目的志向的で先を見越して行動がなされる。相手に怒りを持ったとき，直接暴力で傷つけるのは前者であり，相手から金銭を奪うといった行動は後者である。

この二分法は，攻撃行動を説明するモデルとして有用であることが実証されている。縦断的研究により，道具的攻撃を行った者は，後に再び反社会的行動に走りやすく，一方，反応的攻撃を起こした者は，その後むしろ，反社会的行動や道具的攻撃が減少することが指摘されている[32]。典型例として，いじめは道具的攻撃であり，いじめ行動を行う者は，他の場面でもしばしば反社会的行動をとる[34]。

攻撃的な人々を因子分析した結果もやはり，2つの集団に分離されるというものであった[8]。第一に，反応的攻撃だけを示す群である。社会規範に無関心で，状況に応じて自分の行動をコントロールすることができない。こうした人々については，眼窩前頭前皮質および腹内側前頭前皮質の関与が指摘されている(後述)。第二には，反応的と道具的攻撃の両方を示す群である。罪悪感や共感性に乏しく，対人関係上，配慮を持った行動ができない。

いうまでもなく，サイコパスは後者である。衝動的で場当たり的に攻撃行動をとることもあるが，巧みに振舞うことによって，自分自身の目的を達成するために攻撃性が用いられる。そして，サイコパスの決定的な要素は，反社会的行動を示すことではない。重要なのは，情動障害である。情動障害がますます発展したとき，反応的攻撃とともに道具的攻撃が高レベルに達し，極度な反社会的行動へと結びつく。

次項からは，反応的および道具的攻撃の認知神経科学的モデルについて紹介する。

4 反応的攻撃の認知神経科学的説明

前頭前皮質に後天的に外傷を受けた患者は，さまざまな性格や感情の変化をきたす。多幸，失感情，無気力，攻撃性の増大などの症状を示すことが，これまでにも一貫して示されている。こうした症状の中でも，社会行動上の障害と眼窩前頭前皮質あるいは腹内側前頭前皮質損傷の関係が近年になり指摘され，大きな影響がもたらされた。これら事実を説明する社会行動障害モデルとして，代表的症例報告とそれらをもとに導き出された神経心理学的仮説を以下に紹介する。

Somatic marker仮説

EslingerとDamasio[18]は，35歳時に眼窩前頭前皮質髄膜腫切除後，社会行動障害を示した症例EVRを報告した。それまで患者は，商社で働き社会的地位も高く，家庭生活も円満であった。しかし手術後まもなく行動の変化が起こり始めた。EVRは周囲のたびたびの警告にもかかわらず危険な事業に手を出し破産し，離婚を繰り返した。1つの仕事を継続できず，将来の計画を立てる能力を損なった。すなわち，近視眼的(myopia)[17]になった。

EVRの知能，記憶，社会的知識，道徳観念，論理的判断能力などは全く問題なく保たれていたが，何事に関しても感情の喚起が起こらないという情動の欠如が自他ともに認められた。Damasioは，EVRの情動障害が実生活での不完全な意思決定を導いたと考え「somatic marker仮説」を提言した。

われわれは個人的・社会的領域で新しい状況に直面し意思決定を必要とするとき，与えられた数多くの行動オプションに対して，将来の帰結を合理的に推論することのみで意思決定を行っているのではない。Damasio[17]によれば，それら論理的判断に先行してsomaticな状態(情動を含む身体反応)が強く作用し，危険を察知することで，一種のバイアス装置として機能しているとされる。さらに，このような個人的・社会的状況と身体イメージとの結びつきを支えている神経基盤として，腹内側前頭前皮質が主要な役割を演じると考えた。

Somatic marker仮説の流れの中で，Becharaらは，腹内側前頭前皮質の損傷を特異的に検出する神経心理検査としてIowa Gambling Taskを考案した(詳細は文献10参照)。われわれの機能的MRI研究でも，この課題遂行中に，危険予期に関連して，内側前頭前皮質の活動がみられると同時に，その部位の脳活動の強さがタスクの成績と相関するとの結果が得られ，somatic marker仮説と矛盾しない知見が得られた[20]。

Social moral知識獲得仮説

Andersonら[4]は，生後16カ月未満に腹内側前頭前皮質に損傷をきたした患者2例(20歳，23歳)を報告した。患者らは同様に社会行動障害を呈したが，成人後損傷患者のものより重篤な問題行動を示した。

成人期に達してからの損傷においても，さまざまな社会状況での意思決定場面で情動反応や行動に異常がみられるが，少なくともそれまでにすでに獲得した社会的・倫理的知識は温存されている。これに対して，発達初期の腹内側前頭前皮質損傷の場合には，そのような知識を獲得する段階でのコード化が障害されるため，社会的知識そのものが獲得されないと考えた。

つまり，Andersonらは，幼少期のsomatic marker獲得機構の障害が，重度な社会的逸脱行動の基盤にあると解釈し，social moral獲得仮説として提案した。

人の意思決定に，認知のみならず情動の関与を指摘し，また神経心理学的モデルを提示したという点で，これら仮説は非常に示唆的で興味深い。さらに，SaverとDamasio[36]は，EVRの問題行動がDSM-Ⅲの“soiopathic disorder”(社会病質性障害)に相当することから，このような腹内側前頭前皮質損傷による行動異常を“aquired sociopathy”と名づけた。そして，これが，サイコパスの病態のモデルにも当てはまると考えた。

しかし，眼窩前頭前皮質あるいは腹内側前頭前皮質の損傷患者の示す行動を詳細に分析すると，道具的攻撃ではなく，反応的攻撃に強く関与していることが指摘されている[4]。つまり，somatic marker仮説は，サイコパスの示す道具的攻撃をうまく説明できていない。

このことは，後に再度触れることにする。

5 道具的攻撃の認知神経科学的説明

ここで，一般的な発達過程における攻撃性の

獲得について簡潔に述べておく。

幼児では，1歳頃を起点として，物を投げる・壊すといった物理的破壊行動から攻撃性が始まる。ことばを覚えるにしたがって，2，3歳ごろより言語的攻撃性が現れる[14]。その後，いったん攻撃性は収まる方向に向かうが，一部の児童で攻撃性が持続し，学級などで問題となる。8歳以降では，攻撃性は，身体的，言語的，間接的といった順に表出されてくることが報告されている[35]。間接的攻撃については，女児に比較的特徴的で，自分の目的達成のために他者を操作するような行動であり，悪口を言ったり，仲間はずれにすることで，相手を社会的に排除することなどが例としてあげられる[16]。いうまでもなく，これは道具的攻撃である。

攻撃性は，年齢を経て，言語を獲得して，反応的攻撃から道具的攻撃へと次第に形を変えていく。反応的攻撃は生得的要素が強く，道具的攻撃は獲得的要素が強い[12]。さらに，道具的攻撃の獲得には，社会性が必要である[37]。社会認知能力が上がれば上がるほど，反応的攻撃は道具的攻撃へと置き換わる。つまり，道具的攻撃は，社会的学習の結果であるともいえる。他者に対してたまたま用いた道具的攻撃により自分の欲求が満たされたり(強化)，他者が攻撃行動を使うことで目的を達成するのを目撃することによって(代理強化)，学習する。

近年，扁桃体の機能について飛躍的に理解が進み，情動形成に関連する神経システムが明らかになってきている。それに基づき，以下に，反応的・道具的攻撃性の神経機構について整理を行う。

統合的情動システムモデル

扁桃体は大きく中心核と基底外側核に分けられる。そのうえで，以下の3つの回路に分類される。これは情動的統合システム(Integrated emotion system)と呼ばれている[33]。

①さまざまな感覚入力を受けることによって，感覚形成の調節を行う(中心核，外側基底核)。

②脳幹に投射することにより，情動刺激に反応して内臓機能の調整に関与する(中心核)。

③前頭葉を主とする前脳領域とのコネクションを介して，目的志向性行動に影響を及ぼす(外側基底核)。

例えば，目の前に相手が現れ，挑発してきたとする。われわれは，視覚，聴覚，嗅覚などさまざまな感覚から状況や情報を収集して，相手の体格，姿勢，態度，精神状態，意図，緊急度などを瞬時に処理し統合しなければならない。そのうえで，怒りという情動を呼び起こすべきである事態だとラベリングをする(①)。

次に，怒り情動が喚起されると，視床下部，下垂体，副腎皮質などを経由して内分泌系の活動を亢進させる。また，中脳，延髄を通して，自律神経系を興奮させる。つまり，怒りの対象を認識することによって，エネルギーを最大限に注いで，攻撃行動に移れるように身体の各部位を調節する(②)。

しかし，怒りにまかせて即時的に行動(反応的攻撃)するだけではない。対象に関する得られた情報を，過去の経験や社会的な文脈などと照らし合わせて評価し，行動のプランを作成する。それにより，攻撃を一時的に抑制し機会をうかがったり，他の行動の選択肢の検討を行う場合もある。つまり，情動を主体的にコントロールする(③)。これこそが，道具的攻撃の成立の核心である。

このように，扁桃体は，入力された感覚を受けて統合し，情動の方向づけを行っていると考えられている。

しかし，ここまで述べたことは，人が生存していくうえで必要不可欠なものである。他者から脅かされたときに，攻撃性が全くなければ，その人はただちに淘汰されてしまうであろう。攻撃性そのものは，反応的であれ道具的であれ，決して悪ではない。

それに対して，サイコパスは，些細なことでいら立ち，衝動的に破壊行動を行い，行動のコントロールができない。一方で，自らの欲するものを手に入れるために，共感性や情緒性を伴うことなく，やすやすと嘘，偽りでもって他人を欺く。つまり，感情的で抑制不能な反応的攻撃性を示すと同時に，非常に巧みかつ肥大化した道具的攻撃性を持ち合わせる。

では，人のもつ攻撃性を社会に適応的にするか，そうでないか，ということに導く要因は何であろうか？

6 サイコパスの病態は何なのか？

人および動物における扁桃体の損傷研究が，サイコパスを考えるうえで示唆的である。扁桃体の損傷患者では，嫌悪条件づけ[11]，驚愕反射[5]，受動回避学習[3]，表情認知(特に恐怖表情)[1]が障害される。サイコパスに対してこれらの数々の神経心理学的検査を行った結果は，扁桃体損傷患者のデータとよく合致する[26]。

さらに，最近のイメージング手法によっても，サイコパスと扁桃体の障害との関連が，これまでに3つ報告されている。

Tiihonenら[38]は，サイコパスを対象として扁桃体の体積とPCL-Rの点数との相関をMRIを用いて調べた。PCL-Rの点数が高い群では，健常群と比較して右の扁桃体の体積が減少しており(21%)，PCL-Rの点数と有意に負の相関がみられた。

Kiehlら[27]は，情動的記憶課題を用いて機能的MRI実験を行った。サイコパスに不快な単語を記憶させたところ，中性的な単語を記憶させた場合と比較して，扁桃体，海馬，海馬傍回，腹側線条体，前・後帯状回において活動の低下がみられ，両側の前頭側頭皮質において活動の上昇がみられた。

Veitら[39]は，情動学習に関与する部位を，機能的MRIを用いて調べた。その結果，恐怖表情刺激に対して，サイコパスは健常者および社会恐怖患者と比較して，有意に眼窩前頭前皮質，島，帯状回，右の扁桃体において脳活動の低下がみられた。

以上のように，サイコパスの示す一般的な情動処理障害については扁桃体の器質的・機能的障害として説明可能である。

しかし，ここで4節で述べた眼窩前頭前皮質障害と同様の問題に直面する。というのは，成人の扁桃体損傷患者では，反応的攻撃は示しても，道具的攻撃はみられない[13]。つまり，眼窩前頭前皮質損傷と同様に，道具的攻撃を説明できない(幼少期の扁桃体損傷患者についてはそうではない[19])。

これらのことから，発達早期の扁桃体の器質的・機能的障害が関与しているとの仮説が，近年，有力視されている。

Moral socialization障害仮説

扁桃体は，刺激と報酬・罰との関連づけの形成に，重要な役割を果たしていることがわかっている[9]。健全な発達では，攻撃を用いることで及ぼした，被害者の恐怖や悲しみの表出に反応し，自らの道徳的逸脱行動によって，被害者に苦痛を与えたということを理解する。つまり，負の条件刺激(例えば，相手を傷つけること)と負の条件反射(例えば，相手の苦しむ表情をみること)との連関が学習される。そうすることで，被害者の感情に注意が向き，共感性が発達する。情緒反応性，共感性，他者への基本的信頼感などが，道具的学習と組み合わさることで，良好な社会適応へと繋がる。一方で，扁桃体に機能不全がある者，つまり恐怖感情に対する反応が乏しい者は，他人の嫌悪という苦痛を見つけることができず，適切な連関が学習されない。Blairは，この嫌悪条件づけの失敗が，社会的不適応へと導いていると考え，Moral socialization障害仮説として提案した[13]。

この仮説によると，サイコパスは，発達早期に扁桃体に器質的・機能的障害があることが想

定される。それにより，社会の一員として必要な知識や習慣を身につけていく過程自体が障害されているため，暴力行動の抑制がなされず，反応的・道具的攻撃を示し，また共感性や道徳なども育まれないとされる。

ここまで述べたように，近年の知見をふまえると，サイコパスは，発達早期の扁桃体機能不全であるというのが，暫定的ではあるが，本稿の結論である。

しかし，これに加えて，眼窩前頭前皮質ないし腹内側前頭前皮質の障害の合併も考慮に入れるべきだとの指摘がなされている。根拠として，これら部位の障害を特異的に検出するとされる，Iowa Gambling Taskやリバーサルラーニング課題において，サイコパスの患者群の成績が悪いことがあげられる[30]。また，眼窩前頭前皮質および腹内側前頭前皮質は扁桃体との神経のコネクションが豊富な部位である[2]。これらの知見から，Blairは，幼少期における扁桃体の器質的・機能的障害が，これら前頭葉に二次的に障害を及ぼしていると考え，その過程にノルアドレナリン系の関与を推定した[13]。

これら仮説は興味深い。しかし，実証に至るためには，今後さらに，幼少期扁桃体損傷例の蓄積，コホート研究，受容体イメージング，遺伝子レベルの研究などが必要であろう。

7 さいごに

京都医療少年院において，これまで筆者は，矯正の現場で臨床にたずさわってきた。そのなかで，サイコパスに該当する少年らに接触する機会も少なくなかった。

サイコパスは，衝動的・攻撃的なその行動から，一見“強い”ような印象を与える。しかし，彼らの内面は，自己愛に満ち，傷つきやすく，極めて脆弱である。彼らの示す道具的攻撃，巧みな嘘や偽りという“能力”は，情動の欠如を代償的に補うために，歪んだ認知を発達させたもので，1つの社会的生き残り戦略のようにも思えてくる。

今，サイコパスに対して，わたしたちができることは何であろうか？

現在，サイコパスに対する治療は，困難を極めている。刑務所・少年院における矯正教育プログラムは，原則，認知行動療法に基づいている。しかし，サイコパスが扁桃体機能不全であるとするならば，そうした治療法では効果は期待できない。少年たちに対して行われる認知的アプローチ，すなわち“社会的学習”が，逆説的に道具的攻撃性を増幅させるだけだからである（スーツを着た蛇“snakes in suits”[7]）。事実，その種の治療法は，サイコパスの病態をかえって悪化させることが，これまでにも多数報告されている[23]。

一般医療においても，サイコパスへの治療的介入はほとんどできていないというのが現実であろう。サイコパスと医療の接点は，他害行為による措置入院などだけで，機会はごく限られている。というのも，そもそもサイコパスは，真に治療的意味で精神科に助けなど求めない。また，大阪教育大附属池田小大量殺傷事件をきっかけにして，2005年に「心神喪失等の状態で重大な他害行為を行った者の医療及び観察等に関する法律」（いわゆる医療観察法）が施行された。しかし，“心神喪失とみなされない”“治療可能性がない”などの理由により，現状では本法では，サイコパスや人格障害は治療の対象者にすらならない。

したがって，法律モデルにおいても医療モデルにおいても彼らは見放されている。残された末は，宅間守元死刑囚のように，度重なる犯罪により刑務所や病院の入退院を繰り返し，挙句の果てに凶悪犯罪を働き，最後は死刑になることだけだろうか？そして何よりも，数多くの犠牲者はそれで報われるのだろうか？

サイコパスをどう処遇していくのかという行政上の問題は，簡単に結論が出るものではない。しかし，まずわたしたちがやるべきことは，

サイコパスの病態を明らかにすることではないか。幸い，画像技術の飛躍的な進歩を足掛かりに，それは不可能なことではなくなりつつある。そして，そこで得られた知見を治療へと生かすことこそが，進むべき道ではないか。

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Structural abnormalities of the adhesio interthalamica and mediodorsal nuclei of the thalamus in schizophrenia

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Abstract

Objective: Several studies have suggested the existence of thalamic volume reduction in patients with schizophrenia. However, the precise locus of volume reduction within the thalamus has scarcely been investigated. On the other hand, underdevelopment of the adhesio interthalamica [AI; Danos, P., Baumann, B., Kramer, A., Bernstein, H.G., Stauch, R., Krell, D., Falkai, P., Bogerts, B., 2003. Volumes of association thalamic nuclei in schizophrenia: a post-mortem study. Schizophr. Res. 60 141–155], which bridges bilateral medial edges of the thalamus, has been reported in patients with schizophrenia. We assessed the volumes of mediodorsal nuclei (MDN) of thalami, level of AI development, and their interrelationship, in patients with schizophrenia. Method: A sample of 58 patients with schizophrenia and 44 matched healthy volunteers underwent assessment with high-resolution 1-mm-thick anatomical MRI. Volume measurements of the MDN of the thalamus and whole thalamus were performed by manual tracing. The level of AI development was quantitatively defined as the maximal anterior-to-posterior length of the AI. Results: Schizophrenia patients had significantly smaller volumes of bilateral MDN. AI ratings were twice as high in women than in men among the control subjects; however, no gender difference emerged in the schizophrenia group due to reduced ratings in female patients. No significant correlation was found between MDN volumes and AI ratings among both groups. Conclusions: These results provide evidence of volume reduction of the MDN, and female-specific underdevelopment of the AI in schizophrenia. As we did not demonstrate a relationship between MDN volume and AI ratings, it is suggested that these two measures of medial thalamic abnormality are manifestations of different neuropathological processes in schizophrenia patients.

Keywords: Schizophrenia; Adhesio interthalamica; Thalamus; Psychopathology

1. Introduction

As well as regional cortical abnormalities, medial and midline structural abnormalities, such as volume reduction of the corpus callosum or increased incidence of cavum septum pellucidum, have been repeatedly reported in schizophrenia. Among these midline and

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medial structures, the thalamus has been a region of intensive investigation due to its putative role in the central pathophysiology of schizophrenia. Although some neuropathologic studies (Pakkenberg, 1990) have found thalamic morphological abnormalities, volumetric neuroimaging studies have been inconsistent, with some studies demonstrating volume reductions in chronic (Staal et al., 1998) or first-episode (Crespo-Facorro et al., 2007) schizophrenia subjects, while others have not detected such abnormalities (Preuss et al., 2005). Thus, it could be hypothesized that thalamic abnormalities in patients with schizophrenia might be confined to certain thalamic nuclei.

Among the thalamic nuclei, the mediodorsal nuclei (MDN) are of particular interest, due to their reciprocal connections to the prefrontal cortex (Antoniadis and McDonald, 2006; Volk and Lewis, 2003), a key area of functional and structural alterations in schizophrenia (Harrison, 1999). Post-mortem studies have repeatedly demonstrated MDN abnormalities, including reductions in volume and neuron number in this region (Byne et al., 2002; Danos et al., 2003; Young et al., 2000), in schizophrenia patients. Although *in vivo* visualization of individual thalamic nuclei has been difficult, a recent MRI volumetric study by Kemether et al. (2003) successfully parcellated the MDN, and reported its volume reduction in schizophrenia patients.

Another midline thalamic structure of interest is the adhesio interthalamica (AI; or massa intermedia), which bridges the medial borders of both thalami across the third ventricle. The AI contains several nuclei and interhemispheric fibers. Although the AI is normally well developed in mammals (Snyder et al., 1998), there is a substantial variation in its size in humans. Post-mortem studies have shown that the AI is absent in approximately 20% of humans (Samra and Cooper, 1968; Carpenter and Sutin, 1983), and that it is more commonly absent in males than females (Allen and Gorski, 1991). The functional role of this small structure has not been fully elucidated. However, because of the substantial interindividual variation of the AI in the normal population, several researchers have investigated a possible role for abnormalities of the AI in schizophrenia. As the AI develops at around 13 to 14 weeks of gestation (Rosales et al., 1968), the presence of an abnormality of the AI would indicate a very early brain pathology in schizophrenia. Together with the cavum septum pellucidum, another midline abnormality, a missing AI is not uncommon in normal subjects. Thus, midline structural abnormalities should be regarded as early neurodevelopmental risk factors that could be associated with a future manifestation of schizophrenia rather than as causative determinants of schizophrenia. Several MRI studies have evaluated the presence or absence of the AI in schizophrenia patients; however, results have been conflicting. Snyder et al. (1998) found that the absence of an AI was more common among first-episode patients with schizophrenia than among healthy controls in an MRI study, but did not find these differences among chronic schizophrenia patients in a post-mortem study. Erbagci et al. (2002) reported that the absence of the AI was more common in patients with schizophrenia than in healthy individuals, but Meisenzahl et al. (2000, 2002) and de Souza Crippa et al. (2006) failed to replicate such findings, although Meisenzahl et al. (2000) noted that patients without an AI had more severe negative symptoms than those with an AI. Nopoulos et al. (2001) found that female patients with schizophrenia had a significantly higher prevalence of an absent AI, compared with control females, but when female and male subjects were pooled together, no significant differences emerged. Finally, in a twin study investigating monozygotic twin pairs concordant for schizophrenia, those that were discordant for schizophrenia, and control twin subjects, Ettinger et al. (2007) found no group difference regarding the presence of an AI.

The focus of the present study is as follows. First, we attempted to replicate the finding of MDN volume reduction in schizophrenia patients by Kemether et al. (2003). More specifically, in the present study, we used a 3-T MRI machine to increase the power of visualization of contours of the nuclei. The second purpose of our study was to identify a potential factor causing the conflicting results in the literature regarding AI abnormalities in schizophrenia patients. Previous studies investigating this structure may have lacked adequate statistical power, partly because they employed categorical statistics comparing those with AI and those without. In the present study, the level of AI development was quantitatively defined based on the anterior–posterior maximal length of the AI.

The AI bridges the medial edges of the MDN or its adjacent thalamic nuclei, and consists of several nuclei as well as interhemispheric fibers, among which those connecting bilateral MDN are reported to be the major population (Zawitsch, 1952). Considering such connectivity, it is possible that both of these medial thalamic abnormalities, that is, MDN volume reduction and AI underdevelopment, are correlated in schizophrenia patients. Alternatively, despite the tight connectivity, they might not be correlated because of differences in the timing of the development of these two structures. Thus, in the final part of the current study, we analyzed the interrelationship between these two structural measures.

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2. Methods

2.1. Participants

All subjects were right-handed. The schizophrenia group comprised 64 patients (30 men and 34 women), 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). Thirty-four subjects were diagnosed as having the paranoid subtype of schizophrenia, 13 as having the disorganized subtype, four as being catatonic, three as having the residual subtype, three as having the undifferentiated subtype, four as having schizophreniform disorder, and three as having schizoaffective disorder. All patients were receiving antipsychotic neuroleptics (12 were taking only atypical neuroleptics, 21 were taking only typical neuroleptics and the others were taking combinations of these), and haloperidol equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia (APA, 1997, Woods, 2003). All patients were physically healthy at the time of scanning. None had a history of head trauma, neurological illness, serious medical or surgical illness or substance abuse.

The control group, recruited from the community, consisted of 51 healthy individuals (22 men and 29 women) who were matched for age, gender, handedness and education level with the schizophrenia group. None of them had any history of neurologic 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. In addition, none of them had a family history of mental illness. 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.

Table 1
Demographic and clinical characteristics of the participants

	NC (N=51)	SCZ (N=64)	Statistics
	Mean (SD)	Mean (SD)	p
Age (years)	36.1 (8.4)	36.3 (11.0)	NS
Sex (male/female)	22/29	30/34	NS
Handedness (left/right)	0/51	0/64	NS
Education years	14.1 (2.3)	13.6 (2.2)	NS
Age at onset (years)	–	26.0 (10.1)	–
Duration of illness (years)	–	10.4 (9.1)	–
Drug (mg/day, haloperidol equivalent)	–	14.4 (7.0)	–
PANSS total	–	66.3 (20.2)	–
PANSS positive	–	15.1 (6.3)	–
PANSS negative	–	17.8 (7.0)	–

Abbreviations: PANSS = Positive and Negative Syndrome Scales; NC = normal controls; SCZ = schizophrenia patients.

2.2. MRI acquisition

All participants received MR scans using 3.0-T whole body scanner equipped with a volume head-coil (Trio, Siemens, Erlangen, Germany). The scanning parameters for the three-dimensional magnetization-prepared, rapid-gradient echo (3D-MPRAGE) sequences were as follows: echo time (TE)=4.38 ms; repetition time=2000 ms; inversion time (TI)=990 ms; field of view (FOV)=256×256 mm^2; resolution=0.94×0.94×1.0 mm^3; 208 axial slices of 1.0 mm thickness. In order to increase the signal-to-noise (S/N) ratio, we scanned all subjects three times and made average images from these three images using statistical parametric mapping 2 (SPM2) software (http://www.fil.ion.ucl.ac.uk/spm).

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) (Kay et al., 1987). Estimated verbal and performance IQ scores were obtained from subtasks of vocabulary and block design in WAIS-R, respectively, by transforming scores corrected for age into T scores.

2.4. Thalamic volumetry

Thalamic volumetry was performed by the first author (MS) who was blind to participant details, including the study group, during the measurement. The averaged 3D-MPRAGE images were realigned parallel to the anterior–posterior commissure line and analyzed using MRIcro software (Nottingham, UK). MRIcro permits the manual tracing of regions-of-interest (ROIs) and gives an automatic estimate of their volumes. Tracing of whole thalamus and MDN was performed manually on all slices following the procedure used by Kemether et al. (2003) (Fig. 1a).

2.5. AI ratings

Evaluation of the AI was performed by the first author (MS) who was blind to participant details, including the study group, during the measurement. Initially, images were displayed simultaneously in three orthogonal views

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