Stimuli were randomly presented in order to avoid effects of expectation. The inter-stimulus interval was set within a range of 1500 ± 500 ms. The percentage of targets was 20% (80 out of 400 times). Total experimental time was 13 min and 20 s. Prior to data acquisition the task procedure was fully explained to the subjects, and they were given sufficient practice to understand it.

Parameters of measurement

The following 10 parameters were measured.

The number of cancellations of a target stimulus (T-cancel) was the number of times a subject responded within 150 ms of target presentation onset. The number of cancellations of a non-target stimulus (N-cancel) was the number of times a subject responded within 150 ms of non-target stimulus presentation onset. The shortest response time for detecting the target stimuli is said to be 150 ms.

The number of omission errors (Omission) was the number of times a subject failed to respond to a target stimulus. Hit rate (Hit) was the ratio of accurate responses to the total number of times a target stimulus was presented, and was calculated as (80 – number of cancelled targets – omission errors)/80.

The number of commission errors (Commission) was the number of times a subject responded to a non-target stimulus. The false alarm rate (False) was the ratio of mis-responses to the total number of non-target stimuli, and was calculated as (number of cancelled non-target stimuli + commission errors)/320.

Mean RT for a correct response was the time from presentation of the target stimulus to the reaction. The coefficient of variance of mean reaction time (CVRT) was also determined.

The sensitivity index (d′) reflects a subject's perceptual sensitivity to a target; it is the distance between signal and noise distributions in standard score units, calculated as $z(h) - z(f)$ with z, h, and f equal to normal deviance, hit rate, and false alarm rate, respectively. High d′ indicate high levels of signal detection relative to noise and suggest better discrimination between target and non-target stimuli.

The response criterion index ($\ln\beta$) is a function of a subject's tendency to respond too little or too much relative to the actual distribution of a target, and is calculated as $\ln\{y|z(h)|/y|z(f)|\}$, with y the ordinate of the normal distribution. A $\ln\beta$ of 1 indicates the smallest bias in responding. A $\ln\beta < 1$ indicates that a subject tends to respond to noise (non-target) as a target, while a $\ln\beta > 1$ indicates that he or she tends to respond to the target as noise (non-target).

Statistical analysis

Data were analyzed using the statistical software package SPSS 11.5 J for Windows (SPSS Inc., Chicago, IL, USA). The relationship between age and CPT measurements was examined using one-way analysis of variance (ANOVA) and post-hoc Scheffe's analysis. The significance level was set at $P < 0.05$ (two-tailed).

RESULTS

Tables 1 and 2 show mean scores of CPT indexes by age groups from 5 to 12 years of age.

Cancellation of target and non-target stimuli

There were significant differences in number of cancellations of target stimuli (T-cancel) among the age groups. A post-hoc test showed that T-cancel was significantly higher in the 5-year-old group than in the other age groups. Results for T-cancel exhibited significant change until 5 years of age.

There were also significant differences in number of cancellations of non-target stimuli (N-cancel) among the age groups. A post-hoc test showed that N-cancel was significantly higher in the 5-year-old group than in the other age groups, and significantly higher in the 6-year-old group than in the 9–11-year-old groups. Results for N-cancel exhibited significant change until 6 years of age.

Hit rate, false alarm rate, and omission and commission errors

As shown in Table 1, there were significant differences in hit rate (Hit) among the age groups. A post-hoc test showed that Hit was significantly lower in the 5-year-old groups than in the 6–12-year-old groups, and in the 6-year-old group than in the 7–12-year-old groups. Results for Hit exhibited significant change until 6 years of age.

There were also significant differences in False alarm rate (False) among the age groups. A post-hoc test showed that False was significantly higher in the

Table 1 CPT accuracies (mean ± SD) by age group (5–12 years)

	CPT indexes					
	T-cancel	N-cancel	Hit	False	Omission	Commission
5 years (n = 35)	4.77 ± 9.36^{a}	19.14 ± 38.29^{a}	0.66 ± 0.23^{a}	0.01 ± 0.02^{a}	22.74 ± 16.45^{a}	2.89 ± 4.25^{a}
6 years (n = 42)	1.67 ± 1.57^{b}	9.14 ± 6.19^{b}	0.81 ± 0.12^{b}	0.01 ± 0.01^{b}	13.29 ± 8.65^{b}	1.62 ± 2.00^{a,c}
7 years (n = 78)	0.06 ± 0.89^{b}	2.82 ± 3.36^{b,c}	0.96 ± 0.04^{c}	0.00 ± 0.00^{b}	2.24 ± 2.48^{c}	1.46 ± 1.48^{b,c}
8 years (n = 82)	0.38 ± 0.64^{b}	2.10 ± 2.25^{b,c}	0.98 ± 0.03^{c}	0.00 ± 0.00^{b}	1.52 ± 2.05^{c}	0.90 ± 1.22^{b,c}
9 years (n = 86)	0.26 ± 0.49^{b}	1.23 ± 1.83^{c}	0.98 ± 0.02^{c}	0.00 ± 0.01^{b}	1.27 ± 1.63^{c}	1.37 ± 1.82^{b,c}
10 years (n = 88)	0.22 ± 0.49^{b}	0.67 ± 0.93^{c}	0.99 ± 0.02^{c}	0.00 ± 0.00^{b}	0.75 ± 1.38^{c}	0.96 ± 1.10^{b,c}
11 years (n = 80)	0.06 ± 0.24^{b}	0.36 ± 0.90^{c}	0.99 ± 0.01^{c}	0.00 ± 0.00^{b}	0.63 ± 1.07^{c}	1.28 ± 1.56^{b,c}
12 years (n = 27)	0.00 ± 0.00^{b}	0.19 ± 0.40^{b,c}	1.00 ± 0.01^{c}	0.00 ± 0.00^{b}	0.37 ± 0.74^{c}	0.85 ± 1.17^{b,c}
F (7,510)	16.103*	16.837*	116.580*	6.302*	104.275*	5.351*

Figures with different superscript letters in the same row differ significantly with each other at P < 0.05. (*P < 0.05). n, the number of subjects; T-cancel, the number of cancellations of the target stimuli; N-cancel, the number of cancellations of the non-target stimuli; Hit, hit rate; False, false alarm rate; Omission, the number of omission errors; Commission, the number of commission errors.

Table 2 CPT responses (mean ± SD) by age group (5–12 years)

	CPT indexes			
	RT	CVRT	d′	lnβ
5 years (n = 35)	769.11 ± 57.74^{a}	35.34 ± 27.22^{a}	2.17 ± 1.15^{a}	1.22 ± 0.47^{a}
6 years (n = 42)	737.02 ± 53.22^{a}	22.94 ± 6.09^{b}	2.87 ± 0.67^{b}	1.27 ± 0.36^{a}
7 years (n = 78)	623.41 ± 68.84^{b}	18.79 ± 3.91^{b,c}	4.26 ± 0.67^{c}	0.86 ± 0.67^{a}
8 years (n = 82)	598.74 ± 66.20^{b,c}	17.81 ± 3.44^{b,c}	4.51 ± 0.57^{c,g,i,k}	0.83 ± 0.68^{a}
9 years (n = 86)	551.42 ± 59.92^{d}	18.00 ± 3.79^{b,c}	4.62 ± 0.54^{d,i,k}	0.88 ± 0.77^{a}
10 years (n = 88)	518.94 ± 55.95^{d,e,h}	17.73 ± 3.72^{b,c}	4.82 ± 0.39^{d,h,i}	0.94 ± 0.70^{a}
11 years (n = 80)	418.68 ± 52.43^{f}	16.22 ± 3.36^{c}	4.88 ± 0.38^{e,f,h,i}	0.87 ± 0.63^{a}
12 years (n = 27)	483.37 ± 61.10^{e,f,g,h}	17.15 ± 3.13^{b,c}	5.00 ± 0.31^{d,f,g}	0.93 ± 0.48^{a}
F (7,510)	153.815*	24.755*	132.438*	3.248*

Figures with different superscript letters in the same row differ significantly with each other at P < 0.05. (*P < 0.05). RT, mean reaction time for a correct response; CVRT, coefficient of variance of mean reaction time for a correct response; d′, the sensitivity index; and lnβ, the response criterion index.

5-year-old group than in the other age groups. Results for False exhibited significant change in 5 years of age.

There were significant differences in number of omission errors (Omission) among the age groups. A post-hoc test showed that Omission was significantly higher in the 5-year-old group than in the 6–12-year-old groups, and in 6-year-old group than in the 7–12-year-old groups. Results for Omission exhibited significant change until 6 years of age.

There were also significant differences in number of commission errors (Commission) among the age groups. A post-hoc test showed that Commission was significantly higher in the 5-year-old group than in the 7–12-year-old groups. Results for Commission exhibited significant change in 5 years of age.

Reaction time for correct responses and its coefficient of variance

As shown in Table 2, there were significant differences in mean RT for a correct response among the age groups. A post-hoc test showed that RT was significantly longer in the 5-year-old group than in the 7–12-year-old groups, in the 6-year-old group than in the 7–12-year-old groups, in the 7-year-old group

than in the 9–12-year-old groups, in the 8-year-old group than in the 9–12-year-old groups, in the 9-year-old group than in the 11–12-year-old groups, and in the 10-year-old group than in the 11-year-old group. Results for RT exhibited significant change until 11 years of age.

There were also significant differences in the CVRT for a correct response among the age groups. A post-hoc test showed that CVRT was significantly larger in the 5-year-old group than in the other age groups, and significantly larger in the 6-year-old group than in the 11-year-old group. Results for CVRT exhibited significant change until 6 years of age.

d′ and lnβ

As shown in Table 2, there were significant differences in d′ among age groups. A post-hoc test showed that d′ was significantly lower in the 5-year-old than in the other age groups, in the 6-year-old group than in the 7- to 12-year-old groups, in the 7-year-old group than in the 9- to 12-year-old groups, and in the 8-year-old group than in the 11-year-old group. Results for d′ exhibited significant change until 8 years of age.

There were also significant differences in lnβ among the age groups, though no significant differences in it were noted between groups on post-hoc testing.

DISCUSSION

In the present study, we examined the development of cognitive and attention functions in healthy children using the CPT-X task. We examined a sufficient number of subjects and evaluated a number of indexes to enable easy comparison with findings of previous studies.

The number of cancellations of either the target stimulus (T-cancel) or non-target stimulus (N-cancel) is an index related to the visual recognition of stimuli in a particular CPT. It is believed that this response is based on prediction. In the present study, T-cancel events decreased at the age of 5 years and N-cancel events decreased at the ages of 5 and 6 years, suggesting that development of inhibition of prediction response occurs at these ages.

Failure to control responses to non-target stimuli causes commission errors (Commission) and higher false alarm rates (False), reflecting lack of response inhibition. Previous studies reported that Commission decreased with age.[16–18] Consistent with the results of these studies, in our study Commission decreased significantly at 5 years of age and remained constant thereafter. The development of response inhibition thus appears to reach a plateau at an early age.

The CVRT for correct responses indicates the degree of stability of processing time. This stability improves significantly at 5 and 6 years of age. Thus, the stability of processing time for correct responses also reaches a plateau at an early age.

High numbers of omission errors (Omission) and lower hit rates (Hit) occur due to inattention to target responses. Greenberg and Waldman, and Conners *et al.* showed that Omission decreased with increase in age.[17,18] Further, Lin *et al.* showed that attention function develops during the primary school period.[16] But in the present study Omission decreased more sharply and at a younger age than in the study by Lin *et al.* We thus believe that inattention decreases markedly at these ages.

The mean RT for correct responses includes the processing time from presentation of the target stimulus to reaction. Previous studies using CPT for healthy young subjects showed that RT decreased with age.[16–18] In the present study, RT decreased markedly until 11 years of age.

The sensitivity index d′, developed by signal detection theory,[25] measures discrimination between signal and noise. In the present study d′ increased rapidly up to the age of 8 years. In particular, the rate of change in d′ was very large in children between the age of 6 and 7 years. Lin *et al.* and Conners *et al.* reported that d′ increased with increase in age.[16,18] The present findings are consistent with the results of these studies. Discrimination ability thus appears to increase rapidly until the age of 8 years.

The results of previous studies on the response criterion index lnβ[16,18,19] cannot be directly compared with our own due to differences in task style. This index indicates a subject's tendency to respond too little or too much relative to the actual distribution of task stimuli. Hence, if a subject executes the task correctly, his or her lnβ should be close to 1. In the present study a tendency toward noise reduction was observed in children aged 5 and 6 years, while a tendency toward improved signal detection ability was observed in children older than 7 years of age.

These findings indicate that several response abilities measured by CPT exhibit differences by age. The parameters were correspondingly divided into three

types based on pattern of change: T-cancel, False, and Commission, which are related to inhibition of response; N-cancel, Hit, Omission, which are related to inattention to stimuli; and CVRT, which is related to stability of processing time, all exhibited significant change until 5 or 6 years of age. d', which is related to ability to discriminate between target and non-target, exhibited significant change until 8 years of age. RT, which is related to processing time, exhibited significant change until 11 years of age. Thus, inhibition function, inattention, and stability of processing time develop first. Subsequently, discrimination ability increases based on these developments, and finally processing time is reduced.

One limitation of the present study is its inclusion of female subjects alone. Several studies have demonstrated sex-related differences in CPT performance. Lin *et al.* and Chen *et al.* reported that girls had a lower hit rate, lower d', and higher lnβ than boys.[16,19] In contrast, Conners *et al.* reported that girls had lower omission errors, higher d', and lower lnβ than boys.[18] These reports indicate that findings regarding gender differences in development of attention function are still inconclusive.

We included 5-year-old children in the present study. Although this age group is believed to still have poor conceptual understanding of figures, CPT was a practicable task because the subjects could discriminate between the shapes of the target stimuli. The poor performance of this low-age group is believed to be due to immaturity of attention function and not to poor conceptual understanding of figures.

In conclusion, we assessed CPT-X indexes by age in order to examine the development of cognitive and attention functions during childhood. The findings indicate that development of cognitive and attention functions during childhood can be tracked using CPT parameters. At the age of 5 and 6 years, in particular, marked changes were observed in inhibition function, inattention, and stability of processing time, which are related to abilities to respond. In addition, discrimination ability changed up to approximately 8 years of age. Finally, processing time decreased up to approximately 11 years of age. These normalized CPT data should be useful in evaluating ADHD and other attention-related disorders.

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Regional dopamine synthesis in patients with schizophrenia using L-[β-^{11}C]DOPA PET

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ABSTRACT

The dopamine hypothesis has been the most widely known theory concerning schizophrenia. However, the exact mechanism including presynaptic dopaminergic activity and its relationship with symptom severity still remains to be revealed. We measured presynaptic dopamine synthesis using positron emission tomography (PET) with L-[β-^{11}C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as k_i values, were obtained using a graphical method, and the occipital cortex was used as reference region. Regions of interest were placed on the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). We found significantly higher k_i values in patients than in controls in the left caudate nucleus, but not in the other regions. The k_i values in the thalamus exhibited a significant positive correlation with the PANSS total scores. Furthermore, a significant positive correlation was observed between the PANSS positive subscale scores and k_i values in the right temporal cortex. Patients with schizophrenia showed higher dopamine synthesis in the left caudate nucleus, and dopaminergic transmission in the thalamus and right temporal cortex might be implicated in the expression of symptoms in schizophrenia.

1. Introduction

Positron emission tomography (PET) has allowed us to investigate the dopamine hypothesis in living human brain. Since there is no ideal animal model of schizophrenia, PET investigation is still the most useful method for investigating neurotransmission in patients. As for postsynaptic dopaminergic receptors, several studies have investigated striatal (Farde et al., 1990; Nordström et al., 1995; Wong et al., 1986) and extrastriatal (Suhara et al., 2002; Yasuno et al., 2004) D_2 receptor (D_2R) binding by the use of PET. Although studies investigating D_2R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D_2R binding have repeatedly reported its reduction in the anterior cingulate cortex (Suhara et al., 2002) and the thalamus in schizophrenia (Talvik et al., 2003; Yasuno et al., 2004). Regarding intrasynaptic function, striatal dopamine release was reported to be enhanced in schizophrenia (Breier et al., 1997; Laruelle et al., 1996). On the other hand, many studies did not find any change in dopamine transporter binding in the striatum of schizophrenia (Laakso et al., 2000;

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Laruelle et al., 2000; Schmitt et al., 2005; Yang et al., 2004). These findings suggest that patients with schizophrenia may have elevated presynaptic dopamine synthesis, and investigations on presynaptic dopaminergic function in extrastriatal regions might be critical for providing an understanding of the pathophysiology of schizophrenia.

Radiolabeled L-DOPA, a precursor of dopamine, has been used to investigate presynaptic dopamine synthesis. L-DOPA is transported through the blood–brain barrier (BBB), taken up by presynaptic monoaminergic neurons, and metabolized to dopamine by aromatic amino acid decarboxylase (AADC). Previous studies on the dopamine synthesis of schizophrenia used 6-[^{18}F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashef et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[β-^{11}C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[^{18}F]fluoro-L-DOPA, which is widely used in schizophrenia research, indicated elevated dopamine synthesis (Hietala et al., 1995, 1999; Lindström et al., 1999; McGowan et al., 2004; Reith et al., 1994), elevated dopamine turnover (Kumakura et al., 2007), only higher variability (Dao-Castellana et al., 1997), and even reduced synthesis (Elkashef et al., 2000) in the striatum.

The 3-O-methyl metabolite of L-DOPA crossing the BBB can reportedly cause an error in quantification of the dopamine synthesis rate (Dhawan et al., 1996; Melega et al., 1990; Wahl et al., 1994). However, 3-O-methylation of L-[β-^{11}C]DOPA does not take place readily and rapidly when compared with 6-[^{18}F]fluoro-L-DOPA (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Recently, we evaluated the accuracy of quantitative analyses of L-[β-^{11}C]DOPA PET studies (Ito et al., 2006). In the current study, we investigated regional dopamine synthesis and its relationship with the severity of positive and negative symptoms in patients with schizophrenia using L-[β-^{11}C]DOPA.

2. Methods

2.1. Participants

Fourteen (8 males and 6 females) drug-naïve and 4 (2 males and 2 females) 3-month drug-free patients (35.6± 7.4 years, mean±SD) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia or schizophreniform disorder were recruited from the outpatient units of university hospitals, their affiliated psychiatric hospitals, and a mental clinic. On the day of the PET study, the diagnosis was re-evaluated by 3 experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The severity of psychotic symptoms was also evaluated by the same 3 psychiatrists with the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Igarashi et al., 1998). Each interview was conducted by 2 of 3 authors (S.N., F.Y., M.O.) and one other psychiatrist. Patients with schizophreniform disorder (2 males and 2 females) at the time of the PET study were followed up for at least 6 months from onset, confirming that they eventually met the criteria of schizophrenia. Twenty (10 males and 10 females) healthy volunteers (35.1±9.5 years) were recruited as controls through public notices. All the subjects were examined by physicians to obtain data concerning their educational background as well as current and past medical problems, and family history by unstructured interview and a general questionnaire. Handedness was assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971). The control subjects were matched with the patients for age, gender, education, and handedness. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. The demographic characteristics of all participants are shown in Table 1. Exclusion criteria of patients and controls were as follows: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse including alcohol; (3) previous episodes of mood disorder. One patient was excluded because of a large cyst in the cerebellum (data not shown).

After giving explanation of the study, written informed consent was obtained from all patients and control subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET study

All the participants were instructed to fast for 4 h before PET scan in order to avoid the influence of the plasma concentration of neutral amino acid (NAA) on the L-[β-^{11}C]DOPA uptake rate. A PET scanner (ECAT EXACT HR, CTI-Siemens, Knoxville, TN), providing 63 planes with an axial field of view of 15.5-cm, was used. A head fixation device (Fixster, Stockholm Sweden) was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Data acquisition was performed in 3-dimensional mode with the interplane septa retracted. A bolus of 331.5 to 401.8 MBq (373.0±14.1 MBq, mean±SD) of L-[β-^{11}C]DOPA with specific radioactivities (9.9–156.4 GBq/μmol) was injected intravenously via the antecubital vein and flushed rapidly with 20 mL of saline. Dynamic scans were performed for 64 min immediately after the injection. The scanning sequence consisted of seven 1-min frames, five 2-min frames, four 3-min frames, and seven 5-min frames. All emission scan data were reconstructed with a Hanning filter with a cutoff frequency of 0.4 (final in-plane resolution: 7.5 mm full width at half maximum).

Table 1
Demographic and clinical characteristics of patients with schizophrenia and normal controls

	Controls (n=20)	Patients (n=18)
Gender, M/F	10/10	10/8
Age, y, mean±SD	35.1±9.5	35.6±7.4
Range	20–55	20–52
Medication, no. naïve (M/F)/free (M/F)		14 (8/6)/4 (2/2)
Handedness, no. right/left	20/0	18/0
Education, y, mean (range)	15.1 (12–9)	14.1 (9–16)
No. of smokers (M/F)	4 (4/0)	6 (4/2)
Duration of illness, mo, mean (range)		26.4 (1–120)
PANSS		
Whole score		
Mean±SD		79.2±21.4
Range		46–124
Subscales		
Positive (mean±SD)		22.6±7.3
Negative (mean±SD)		17.1±6.5
General psycho (mean±SD)		39.6±11.0

Table 2
k_i values of each ROI in patients with schizophrenia and normal controls

Region	L/R	Controls	Patients	ANCOVA#	
		(n=20)	(n=18)	F	p
Parahippocampus	L	4.54±1.13	4.91±1.45	0.704	0.407
	R	4.76±1.11	4.47±1.29	0.528	0.472
Temporal cortex	L	1.92±0.99	1.98±0.81	0.041	0.842
	R	1.86±0.83	1.92±0.87	0.037	0.849
Prefrontal cortex	L	1.31±0.73	1.22±0.64	0.324	0.573
	R	1.35±0.73	1.35±0.57	0	1.000
Thalamus	L	3.55±1.60	3.19±1.72	0.549	0.463
	R	3.11±1.45	3.09±1.54	0.001	0.970
Putamen	L	15.52±2.04	15.76±2.14	0.139	0.711
	R	15.39±2.31	14.90±3.01	0.329	0.570
Caudate	L	12.89±2.68	14.66±2.38	4.409	0.043*
	R	13.71±2.74	13.59±2.09	0.026	0.872
Anterior cingulate	L	2.74±1.33	3.05±1.50	0.445	0.509
	R	3.24±1.73	3.00±1.13	0.288	0.595

Dopamine synthesis rates, expressed as $k_i \times 1000$, were presented as mean± standard deviation.
#: Analysis of covariance with age as covariate (df=1, 35).
L indicates left and R indicates right. The symbol * represents $p<0.05$.

2.3. Magnetic resonance images

For each participant, a structure magnetic resonance (MR) image was obtained. All MR imaging studies were performed with a 1.5-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, TE: 9.2 ms; repetition time, TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256×256; slice thickness: 1 mm).

2.4. Data analysis

All MR images were coregistered to the PET summation images of all frames using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROIs) were drawn on the coregistered MR images, referring to the human brain atlas (Mai et al., 1997), and then transferred to the PET images. ROIs were defined for the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. The ROIs were set on both left and right sides of the brain and those values were independently evaluated. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

The overall uptake rate constant k_i of L-[β-^{11}C]DOPA, which indicates the net dopamine synthesis rate, was determined for each ROI by the graphical plot analysis method developed by Gjedde and Patlak (Gjedde, 1982; Ito et al., 2006; Patlak and Blasberg, 1985). k_i values can be estimated by simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F_{t>t^*}$$

where C_i is the total radioactivity concentration in a brain region that can be measured by PET, C_i' is the total radioactivity concentration in the reference brain region with no irreversible compartments, and t^* is the equilibrium time of the compartment for unchanged radioligand in the brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after the time t^*, yields a straight line with the slope k_i and intercept F. In the present study, the occipital cortex was used as reference region (Ito et al., 2006). A range of equilibrium time t^* of 31.5 to 61.5 min was used.

ROI analyses were independently performed by 3 researchers who were blinded to the diagnoses. The intraclass correlation coefficient across all ROIs was 0.976 (McGraw and Wong, 1996), considered as excellent. In order to reduce variance, the k_i values by one researcher that most frequently showed medium values among those obtained by the 3 researchers were used for the following analyses.

2.5. Statistical analysis

Demographic variables were compared by independent sample t-test or chi-square test. Differences in the k_i values for each of the 7 × 2 brain regions between patients and controls were evaluated by one-way univariate analyses of covariance with age as a covariate, since an effect of age on k_i values has been reported (Ota et al., 2006). Pearson's correlation coefficients were calculated between the PANSS scores and k_i values. A significance level of $p<0.05$ (two-tailed) was used both in the comparison analyses between groups and in the correlation analyses.

3. Results

3.1. Demographic data

The demographic data of schizophrenia patients and controls are shown in Table 1. There were no significant differences between patients and controls in terms of age, gender, education, handedness, and the injected dose and

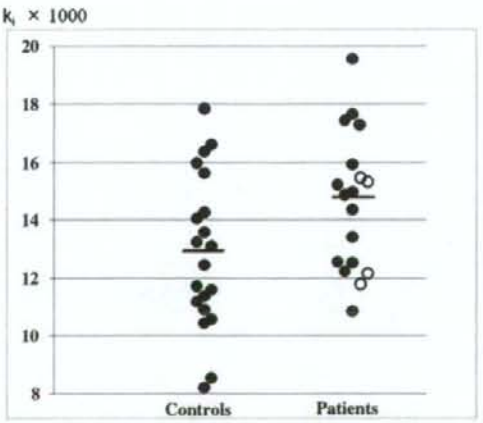

Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those of drug-free patients.

Table 3
Correlations between k_i values of each ROI and PANSS scores in schizophrenia

Region	L/R	Total scores		Positive symptoms		Negative symptoms		General symptoms	
		r	p	r	p	r	p	r	p
Parahippocampus	L	−0.003	0.992	0.045	0.859	0.080	0.752	−0.083	0.745
	R	0.284	0.253	0.288	0.246	0.197	0.434	0.245	0.328
Temporal cortex	L	−0.088	0.728	0.133	0.598	−0.049	0.848	−0.232	0.355
	R	0.465	0.052	0.603	0.008*	0.242	0.334	0.361	0.141
Prefrontal cortex	L	0.380	0.120	0.288	0.246	0.339	0.168	0.346	0.160
	R	0.407	0.094	0.302	0.082	0.457	0.057	0.320	0.196
Thalamus	L	0.620	0.006*	0.490	0.039*	0.504	0.033*	0.589	0.010*
	R	0.470	0.049*	0.378	0.122	0.492	0.038*	0.372	0.129
Putamen	L	0.247	0.323	0.177	0.482	0.342	0.165	0.160	0.525
	R	0.359	0.143	0.327	0.186	0.407	0.094	0.240	0.338
Caudate	L	0.287	0.323	0.294	0.236	0.319	0.197	0.174	0.490
	R	−0.183	0.468	−0.223	0.375	0.021	0.935	−0.220	0.380
Anterior cingulate	L	−0.270	0.120	0.202	0.421	−0.418	0.085	−0.412	0.089
	R	0.355	0.149	0.421	0.082	0.303	0.222	0.231	0.357

L indicates left and R indicates right.
The symbol * represents $p<0.05$.

specific radioactivity of L-[β-^{11}C]DOPA. The duration of illness and the PANSS scores are also shown in Table 1.

3.2. Regional L-[β-^{11}C]DOPA uptake in schizophrenia and control subjects

Univariate analysis of covariance revealed no significant interaction between group and age in any of the regions, and a significant group difference in k_i values only for the left caudate between normal controls and schizophrenia patients was observed ($df=1, 35$, $F=4.409$, $p=0.043$; Table 2 and Fig. 1). In addition, no significant difference was observed in the k_i values between antipsychotic drug-naïve and drug-free patients in any of the regions.

Furthermore, there was no significant correlation between the k_i values in any ROIs and the duration of illness in patients.

3.3. Severity of positive and negative symptoms and L-[β-^{11}C] DOPA uptake

Relationships between k_i values in each ROI and the PANSS total and subscale scores are presented in Table 3. Significant positive correlations were observed between the k_i values in both sides of the thalamus and the PANSS total scores (left: $r=0.620$, $p=0.006$; right: $r=0.470$, $p=0.049$). With regard to PANSS subscales, the k_i values in the left thalamus correlated positively with the PANSS positive, negative, and general symptom subscales, and those in the right thalamus correlated with the PANSS negative symptoms. In addition, a positive correlation was observed in the right temporal cortex between the k_i values and the PANSS positive subscale scores ($r=0.603$, $p=0.008$).

4. Discussion

In the present study, we found increased dopamine synthesis in the left caudate nucleus in patients with schizophrenia compared to normal controls. In addition, we observed a significant correlation between regional dopamine synthesis in the thalamus as well as in the right temporal cortex and symptom severity in patients.

Most of the previous studies with 6-[^{18}F]fluoro-L-DOPA have reported elevated dopamine synthesis mainly in the striatum of patients with schizophrenia (Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994), whereas decreased (Elkashef et al., 2000) or only greater variability (Dao-Castellana et al., 1997) have also been reported in this region. There are some plausible explanations for these inconsistent results. First, the participants with schizophrenia in these studies were not homogeneous. For example, one study investigated heterogeneous patients with psychosis (Reith et al., 1994), while the other studies included patients with schizoaffective disorder (Hietala et al., 1995, 1999). Furthermore, schizophrenia patients on antipsychotic medication participated in two of the PET studies (Elkashef et al., 2000; McGowan et al., 2004). Interestingly, a study on only unmedicated schizophrenia patients showed only greater variability in k_i values compared with normal controls (Dao-Castellana et al., 1997). Second, the differences between 6-[^{18}F]fluoro-L-DOPA and L-[β-^{11}C]DOPA in terms of 3-O-methyl metabolite of L-DOPA crossing the BBB might also result in such inconsistency (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Kumakura et al. reported a method to reduce this problem with metabolites and demonstrated that catabolism and elimination of 6-[^{18}F]fluoro-L-DOPA was elevated nearly 2-fold in the striatum in 8 patients with schizophrenia as compared to that in 15 age-matched control subjects. They concluded that not only the synthesis but also the turnover of radiolabeled dopamine was increased in patients with schizophrenia (Kumakura et al., 2007).

Lindström et al. (1999) investigated unmedicated schizophrenia patients using L-[β-^{11}C]DOPA and found increased dopamine synthesis in the striatum and medial prefrontal cortex, while we observed elevated dopamine synthesis only in the left caudate. As for differences between the two studies, however, the patients in the study of Lindström et al. had relatively more severe psychotic symptoms (Clinical Global Impression ≥4) than our patients. In addition, our patients were mostly outpatients, and thus, such a difference in the demographic of patients might be responsible for the difference in results. In addition, the caudate nucleus might be more important than the putamen in the pathophysiology

of schizophrenia because the caudate has extensive interconnections from the limbic and cortical areas, which play crucial roles in the regulation of cognition and emotion compared to the putamen (Parent, 1990). Further, lateralization to the left of the caudate is consistent with the reports by Hietala et al. (1995, 1999).

With regard to the relationships with symptoms, in our patients, presynaptic dopamine synthesis in the thalamus was positively correlated with overall symptom severity, although that in the right thalamus was correlated only with PANSS negative scores, besides the PANSS total scores; in addition, dopamine synthesis in the right temporal cortex was positively correlated with positive symptoms. The thalamus has been repeatedly reported to be engaged in the pathophysiology of schizophrenia (Clinton and Meador-Woodruff, 2004; Takahashi et al., 2006). Previous neuroimaging studies have shown altered thalamic perfusion and metabolism (Andreasen et al., 1997; Buchsbaum et al., 1996; Clark et al., 2001; Hazlett et al., 1999, 2004; Kim et al., 2000; Mitelman et al., 2005; Resnick et al., 1988) and decreased dopamine D_2 receptor availability in the thalamus in patients with schizophrenia (Buchsbaum et al., 2006; Talvik et al., 2003, 2006; Yasuno et al., 2004). The thalamus is reported to have a pivotal role in the processing and integrating of sensory information related to emotional and cognitive functions (Clinton and Meador-Woodruff, 2004), and it has also been suggested to have sensory gating function (Carlsson et al., 2000; Takahashi et al., 2006). Further, elevated dopamine transmission in the thalamus was reported to disrupt sensory gating function (Young et al., 1995). Impaired gating function could contribute to both positive and negative symptoms by the inability to automatically "gate out" much redundant and unessential information, leading to irrelevant thought and fragmentation of mind and behavior in schizophrenia (Braff et al., 1999). Additionally, one study with 6-[^{18}F]fluoro-L-DOPA examined before and after 5 weeks of haloperidol treatment for schizophrenia demonstrated that the thalamus was the only structure in which the change of dopamine synthesis was related to improvement in negative symptoms (Gründer et al., 2003). Thus, dopaminergic regulation in the thalamus might be associated with positive and negative symptoms in schizophrenia. However, the contribution of different roles of each side of the thalamus to diverse symptom dimensions remains unclear.

In terms of the correlation between dopamine synthesis in the right temporal cortex and the PANSS scale, our data suggested that higher dopamine synthesis in the right temporal cortex might be associated with the expression of positive symptoms in patients with schizophrenia. Previous functional MRI studies have demonstrated the involvement of the right temporal cortex in some of the positive symptoms such as auditory hallucination (Shergill et al., 2000; Woodruff et al., 1997) and formal thought disorder (Kircher et al., 2002) in schizophrenia. On the other hand, although previous PET (Buchsbaum et al., 2006) and SPECT (Tuppurainen et al., 2003) studies have suggested decreased dopamine D_2R binding in the right temporal cortex, no significant correlation was found between the binding and positive symptoms. Furthermore, no study has demonstrated the relationship between presynaptic dopamine synthesis in the right temporal cortex and positive symptoms.

There are several limitations in the present study. First, smoking is regarded as a confounding factor in the estimation of k_i values (Salokangas et al., 2000), and some of our participants were smokers, although the smoking rate of the patients was only slightly higher than that of the normal controls (33% for patients and 20% for controls). Second, our patients consisted of both males and females, although we selected age- and gender-matched control subjects. Laakso et al. (2002) indicated gender differences in striatal dopamine synthesis with the use of 6-[^{18}F]fluoro-L-DOPA PET. However, we did not find such differences in our subjects (data not shown). Nonetheless, since gender differences have been suggested in schizophrenia (Salem and Kring, 1998), this issue should be addressed in future studies. Finally, although our sample size is hitherto the largest among reported studies on dopamine synthesis in schizophrenia, the current study may still not have enough power. Our results of both comparison and correlation analyses were significant only when uncorrected for multiple comparisons, and the failure to observe significant correlations with symptoms in other regions might be due to a type II error. Therefore, further investigations using still larger samples are required.

5. Conclusion

We measured the dopamine synthesis rate in patients with schizophrenia and normal control subjects by using PET with L-[β-^{11}C]DOPA. Patients had higher dopamine synthesis in the left caudate nucleus than controls, which was in line with the results of most previous studies that indicated an increase in dopamine synthesis in the striatum. Moreover, correlation analyses between k_i values and symptoms suggested that dopamine synthesis in the thalamus and right temporal cortex might be implicated in the pathophysiology of schizophrenia. There is little evidence concerning extrastriatal presynaptic dopaminergic functions of schizophrenia in vivo. Further studies are required to better understand the presynaptic dopaminergic functions of schizophrenia.

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Contributors

S. Nozaki, F. Yasuno, A. Takano, and T. Suhara designed the study and wrote the protocol. S. Nozaki, M. Kato, F. Yasuno, M. Ota, A. Otsuka, and Y. Okubo recruited the patients and made psychiatric evaluations. S. Nozaki, H. Takano, M. Okumura, R. Arakawa, R. Matsumoto, and Y. Fujimura participated in the data analysis. S. Nozaki wrote the first draft of the manuscript. S. Nozaki, M. Kato, H. Takano, H. Takahashi, H. Ito, H. Kashima and T. Suhara had discussions and corrected the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors have no conflict of interest.

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自我障害と陰性症状　生物学的背景

大久保 善朗*

はじめに

近年の画像解析技術の進歩により，現在では一人一人の個人の脳形態やさまざまな脳機能を測定評価することが可能になった。そして画像解析技術を用いて精神疾患の症候や病態の生物学的な背景を探ろうとする研究も盛んに行われている。統合失調症は，そのような画像研究の対象として最も調べられた精神疾患であり，まさに統合失調症の画像研究が精神疾患の生物学的研究をリードしてきたとも言える。本稿では主に画像解析を用いた研究の成果を取り上げて，統合失調症の自我障害および陰性症状の生物学的な背景について論じる。

1．自我障害

自我障害はSchneider Kの一級症状に多く含まれているように，統合失調症の中心症状であるにもかかわらず，後述の陰性症状に比べると，生物学的背景を調べた研究は未だ少ない。その理由として，陰性症状が観察評価によって客観的に捉えるのが容易であるのに対して，陽性症状や自我障害は主観的症状であるため評価が難しいという点が挙げられる。しかしながら，近年の脳機能画像研究によって，自我障害の生物学的背景を明らかにしようとする試みが盛んに行われるようになった。

（1） sense of agency（主体感覚）とフォワードモデル

さて，随意運動の認知神経科学的アプローチによって，自己の内的世界に関する意識・自己意識の神経機構に関する検討が進みつつある[9) 14)]。例えば，

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随意的に腕を動かしているときに，人はその腕が自分の身体であるという感覚 sense of ownership（所有感覚）とその腕を自らが動かしている主体であるという感覚 sense of agency（主体感覚）を持っている。随意運動では，この両者の自己意識が共有されるのに対して，不随意運動や運動を強いられる場合には，自分の身体であるという所有感覚は保たれるものの，自分が主体として身体を動かしているという主体感覚が障害されることになる。この2つの自己意識は随意運動だけではなく，何かを思考するときにも，自分の考えであるという所有感覚と自ら主体として考えているという主体感覚を認めることが可能である。統合失調症の作為体験や思考吹入などの自我障害は，自己所有感覚は保たれるものの自己主体感覚が障害された状態として捉えることができる。

このような自己主体感覚の障害という観点から，Frith CD ら[3) 8)]は，自己意識について認知神経科学的なモデルを構築し，脳機能画像研究を積み重ねた上で，統合失調症症状の生物学的病態モデルとして，自己モニタリング機能の障害を提案している。Frith のモデルは，比較照合システム comparator と呼ばれる仮説的神経システムを含む運動制御に関する古典的理論に基づいている。すなわち，われわれが手を動かすときには，一連の筋肉群に指令が伝えられるが，そのときに同時に，どのような指令を送ったかのコピー（遠心性コピー）が，比較照合または自己モニタリングシステムにあらかじめ伝えられ蓄えられる。一方，実際に手を動かした場合に，その運動に伴って生じる感覚系からの求心性の情報が比較照合システムにフィードバックされる。このときに，どのような運動指令を送ったかという遠心性のコピーとどのよう運動が起きたかという感覚系からの求心性フィードバックが一致することによって自分が主体として手を動かしているという所有感覚が成立する。統合失調症では，どのような運動を起こすかという遠心性コピーが比較照合システムに伝わらない。したがって，遠心性コピーと感覚系からの求心性フィードバックに不一致が生じて，動かした手が自分の身体であるという所有感覚は保持されるものの，その手を自らが動かしているといる主体感覚が消失し，何者かによって手が動かされているという作為体験が起きると解釈できる。Frith のモデルは，実際の運動が起きる前にあらかじめどのような運動が起きるかという遠心性コピーの発信を仮定し，その予期的な遠心性コピーの異常を重視している点でフォワードモデルとも呼ばれる。このモデルでは，運動

を思考に代えることによって思考吹入を，運動を内言語に代えることによって幻聴の発生メカニズムを説明できるという。

Frith らは，被験者がジョイスティックを動かしたときに，モニター上に仮想の手の角度を変化させて提示することによって，その運動を被験者自身が行っているという主体感覚を変化させるタスクを考案した。そしてタスク時の脳賦活を脳機能画像を用いて調べることによって，主体感覚の成立に関わる脳内機構を調べた[6]。その結果，健常群では，運動を自らが行っているという自己主体感覚は，両側の島皮質の賦活と関連していたのに対して，運動が他者によって行われる感覚は，右下頭頂皮質の賦活と関連していた。前島皮質は，体性感覚，視覚および聴覚，運動を制御する遠心性コピーと3つのシグナルを統合することによって自己主体感覚の成立に関与し，下頭頂皮質は身体運動の表象を他者の空間座標系に定位に関与していると思われる。さらに Frith らは同様のタスクを用いて Schneider の一級症状を呈した統合失調症患者の脳賦活を調べている[7]。その結果，統合失調症群では，自己から他者へ主体感覚の変化に対応した島皮質の賦活の変化が認められず，右下頭頂皮質の内，右角回で主体感覚の変化に対応した脳賦活が認められたという。さらに一級症状の症状得点が高い患者ほど右角回の賦活が高い相関が認められたという。

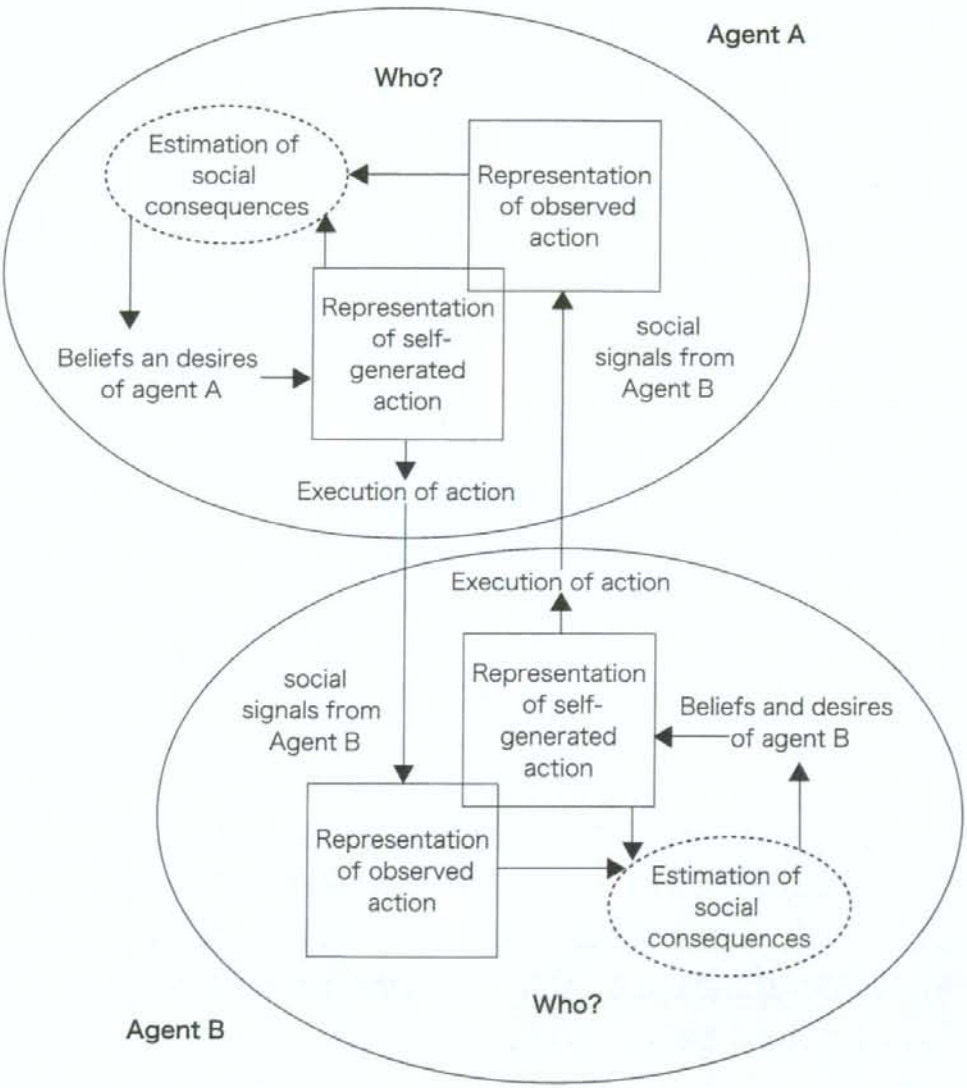
Frith のモデルでは，どのような運動を指令したかという遠心性コピーと照合するために，実際の運動によって生じた感覚系からの求心性フィードバックを必要とする。しかしながら，自分の心の中である動作を想像する場合でも，実際には運動しないので感覚系からの求心性のフィードバックがないにもかかわらず，自ら行っているという想像と，他者が行っているという想像の違い，すなわち主体感覚の違いを区別することができる。このような事象を求心性フィードバックを必要とする Frith のモデルで説明することは困難であるという問題点を指摘することができる。

(2) shared representation（共有表象）と who system

近年の心の理論やミラーニューロンに関連する脳機能画像研究によって，実際には運動はしなくても，自分で運動を想像したり，他者の運動を観察するだけで，運動したときと同様に，運動野，前頭前野，小脳，基底核，後部頭頂葉などの広範な皮質－皮質下ネットワークが賦活されることがわかって

いる[2) 5)]。すなわち，自分の運動の表象条件と，他者の運動の観察条件の賦活を比較すると，どちらの場合においても，前運動野，捕捉運動野および後部頭頂皮質などに共通の賦活が認められる一方で，両条件の賦活の分布には違いも認められるという。

このような脳画像研究の結果から，自己の行動を表象する場合と他者の行



図表は互いを観察する２人の個人（A および B）を描いている。各人は自己の意思または行為と他者の意思または行為の表象をつくる。このとき，自己の行為および観察した他者の行為の表象は重複する。重複が増加するとそれぞれ個人は行為の属性を自己と他者に帰属させることに困難を覚えるようになる。

図１　共用表象と自己と他者の帰属を説明するフローチャート[10)]

動を観察する場合には，共通の表象，すなわち共有表象 shared representation に対応する一定の脳領域の賦活が認められる一方で，両者で共有されない脳賦活も認められるという。したがって両者の異同を判断することによって表象が自己に帰属するのか他者に帰属するのかを区別することが可能になると思われる。このような自己の表象と他者の観察に伴う表象の重なり具合の如何によって，表象が自己か他者に属するかが決定するという「who system」と呼ばれるモデルが提案されている（図 1）[10]。

このモデルを用いることによって，運動に伴う求心性フィードバックがない，想像や表象という心的活動時の，自己か他者かの主体感覚に関連する神経基盤を特定できると思われる。実際に，被験者に対し，自分で行動することを想像させた一人称条件と，他者が同じ行動を行っていることを観察させた三人称条件の脳賦活を比較した研究では，両条件に共通の賦活を認めた一方で，一人称条件では左下頭頂皮質で，三人称条件では右下頭頂皮質で特異的な脳賦活を認めたという。Frith らのモデルとは異なるアプローチであるが他者の行動であるという自己主体感覚が低下する条件で，Frith らが観察したと同様に右下頭頂皮質で賦活が強まるという結果が報告されており興味深い。

さて，統合失調症における自我障害については，神経回路障害によって共有表象を担う神経機構の過剰に活性化され，自己か他者かの帰属判断が障害された病態や，自己か他者かの帰属の区別が障害された病態を想定することができる。このように「who system」は統合失調症の自我障害を考える上で有用なモデルであるが，その異常の病態と考えられる神経回路障害の実態は未だ明らかになっていない。ドパミンの過剰伝達または調節不全により神経回路の異常な興奮が Salience（顕現性）を亢進させ統合失調症の幻覚や妄想になるという Salience 仮説 [11] をあてはめると，ドパミンの過剰伝達により共有表象に関する神経回路の異常な興奮が共有表象の Salience を高め自我障害をもたらすと考えることができる。今後の検証が期待される。

2．陰性症状

統合失調症の症状を陽性症状と陰性症状に分ける考え方は，人間の心的機能に低次から高次までの層構造を想定し，高次機能が低次機能を抑制しつつ

統合機能するというJackson理論に端を発する。Jackson理論によると，陰性症状は高次機能の機能低下による症状であり，陽性症状は高次機能の機能低下によって抑制をはずされた低次機能が産出性の精神症状として表れたものと捉えられる。このように本来は人間の心的機能の層構造に関するJackson理論を背景に持つ陽性－陰性の区別であったが，やがて，幻覚，妄想などの産出性の症状を陽性症状，それ以外の非産出的症状を陰性症状と捉える症候学的な記述用語として用いられるようになった。

(1) Crow TJの二症候群仮説

このような記述的な用語としての使用が広まった1つの理由として，統合失調症の症状を陽性症状と陰性症状の二症候群に分け，それぞれに異なる病理過程を想定するCrowの二症候群仮説（表1）[4]の影響が指摘されている。Crowの二症候群仮説は以下のとおりである。ドパミン放出を亢進するアンフェタミンの乱用が急性妄想型統合失調症様の症状を引き起こすこと，抗精神病薬の臨床効果とドパミン遮断作用が相関することから，統合失調症ではドパミン過剰伝達が考えられる。そしてドパミン過剰伝達に対応する病理所見として，線条体におけるドパミン受容体密度の増加が死後脳研究において確かめられている。抗精神病薬は急性統合失調症の主要症状である陽性症状（妄想，幻覚，思考障害）に対して効果を示す。しかしながら，慢性統合失調症，特に入院患者に主に認められる陰性症状（感情の平板化，会話の貧困化，発動性欠如）に対しては無効なことが多い。慢性統合失調症の基本的な障害は急性統合失調症の障害と異なるという根拠は他にもある。アンフェタミンによって急性統合失調症は容易に悪化するのに，慢性統合失調症は比較的影響を受けにくい。さらに，慢性統合失調症では器質性障害に見られる認知障害を認めることがある。また，気脳写を用いた研究において統合失調症患者

表1　Crowによる統合失調症の二症候群[4]

	タイプⅠ	タイプⅡ
特徴的症候	妄想，幻覚，思考障害（陽性症状）	感情の平板化，会話の貧困化，発動性欠如（陰性症状）
一般的病型	急性統合失調症	慢性統合失調症
抗精神病薬への反応	良好	不良
転帰	可逆的	不可逆的？
知能障害	無し	時にある
想定される病態	ドパミン受容体の増加	脳の細胞消失と構造変化

の脳室拡大が報告されており，Crow ら自身が行った統合失調症の CT 研究においても，脳室拡大が強いものほど陰性症状および知的障害が強い相関が認められた。したがって，統合失調症は 2 つの症候群に分けられ，それぞれが異なる病理過程を持つと考えられる。まず，急性統合失調症と同義であり，陽性症状で特徴付けられるタイプⅠの病理過程としては，ドパミン神経伝達の異常，すなわち，ドパミン受容体の増加が想定される。一方，陰性症状中心のタイプⅡの病理過程は，ドパミン神経伝達にあるのではなく，神経細胞の消失や脳構造の異常にある。以上が二症候群仮説の概要である。

Crow の二症候群仮説の魅力は，単に症候を記述するだけではなく，その症候の背景にある病態について最新の生物学的知見をもとに考察して，統合失調症の中に異なる症候群を特定しようとした試みにある。統合失調症の症状は二症候群のみで記述できるほど単純ではない。しかしながら統合失調症に複数の病理過程とそれに対応した症候群が存在するという Crow のアプローチは，症状を記述的に捉え，治療への反応性や予後などの臨床所見，画像などの生物学的所見などの科学的な証拠を総合的に解析することによって疾病過程を明らかにしようとするものであり，1980 年代以降の統合失調症研究を大いに啓発した。

(2) 陰性症状の画像所見

Crow は陰性症状の病態として CT 研究で明らかになった脳室拡大などの脳の器質変化を想定した。画像解析技術の進歩により，CT 研究から MRI 研究に時代は移り，すでに多数の MRI 研究が統合失調症における脳実質の形態異常を確認している。著者は以前に，統合失調症の脳形態異常と症候との関連を調べた MRI 研究を検討したところ，陰性症状との関連を調べた研究が最も多く，陰性症状は，脳室体積と正の相関を認め，脳の実質と相関については，頭蓋，大脳，灰白質，前頭葉，尾状核，脳梁，側頭葉など多様な部位の面積または体積と負の相関を示していた[15]。この結果からすると，陰性症状の病態として脳形態異常が関連しているとしても，陰性症状を 1 つの脳部位の形態異常に特定するのは困難と思われた。

陰性症状に関連した脳画像所見としては，前頭部における局所脳血流代謝の低活性 hypofrontality がある。統合失調症の前頭部低活性は，陰性症状，特に精神運動貧困（会話の貧困，感情の平板化，運動減退）と負の相関を示すと

いう数多くの報告があり，統合失調症の症状と画像診断の関連としては，最も繰り返し追試されてきた確かな所見と思われる。

陰性症状と前頭部低活性が相関していたとしても，陰性症状が，前頭葉の局所異常のみによって生じているのか否かという点については異論がある。統合失調症患者の症状の因子分析から，精神運動貧困（会話の貧困，感情の平板化，運動減退からなり陰性症状に相当），解体（不適切な感情，思考障害，会話内容の貧困），現実歪曲（幻聴，妄想）の3因子を抽出し，局所脳血流との関連を調べた報告[13]では，精神運動貧困が尾状核と正，左背外側前頭前野，左上頭頂連合野と負の相関，解体が右前帯状回と正，角回，右腹外側前頭前野と負の相関，現実歪曲と左傍海馬回，左腹側線条体と正，右後帯状回と負の相関を示したと報告した。この報告は，陰性症状をはじめとする統合失調症の精神症状が前頭葉だけではなく，辺縁系や連合野や皮質下構造を含む神経回路の異常に基づくものであることを示唆したという。

統合失調症の神経心理学的賦活試験では課題により賦活される大脳皮質に対応して，統合失調症と健常者の群間差を認める部位に違いを認めることがしばしばある。前頭葉機能を賦活する神経心理学的課題時には健常者に比べて統合失調症患者では前頭部の賦活が小さく低活性になることが多くの研究で確かめられている。このような研究では用いる賦活試験に依存して調べられる脳部位が異なることになり，どの脳部位の賦活異常が統合失調症の本質的な病態なのか特定困難である。Andreasen NC ら[1]は，賦活試験によって群間差を認める大脳皮質の分布は異なるものの，視床と小脳においては常に賦活異常を認めることから，視床－皮質－小脳－皮質回路 cortical-thalamic-cerebellar-cortical circuit（CTCCC）の神経回路の連結異常のため，皮質－皮質下の情報の統合に支障をきたしているのが統合失調症の本質的な病態と考えた（認知ジスメトリア：cognitive dysmetria）。同病態によって精神機能の円滑な統合が障害された，さまざまな臨床表現型が説明できるという。

統合失調症の陰性症状，そして前頭部低活性の基礎に前頭前野のドパミン機能の低下を強調する考え方がある。Weinberger DR[17]は，中脳皮質系ドパミン活性低下と中脳辺縁系のドパミン活性の亢進が併存し，統合失調症の陰性症状と陽性症状がそれぞれ起こるという仮説を提唱した。Weinberger は線条体 D_2 受容体拮抗作用の強いハロペリドール服薬中の統合失調症患者において，アンフェタミンが前頭葉機能賦活課題時の血流増加を増強するとと