3.2. Diffusion tensor imaging measures

For FA of the fornix, significant main effects of group ($F[1,94]=3.95$, $p=0.049$) and side ($F[1,94]=24.4$, $p<0.001$) were observed, while the group-by-side interaction was not significant ($F[1,94]=1.60$, $p=0.21$) (Fig. 2, Table 2). For MD of the fornix, significant main effects of group ($F[1,94]=8.96$, $p=0.004$) and side ($F[1,94]=5.60$, $p=0.02$) were observed with no significant group-by-side interaction ($F[1,94]=0.458$, $p=0.50$) (Table 2). These results suggested bilaterally reduced FA and elevated MD of the fornix in patients with schizophrenia compared with control subjects. Of note, no significant interaction between gender and diagnosis was observed (FA: $F[1,94]=0.718$, $p=0.40$; MD: $F[1,94]=0.122$, $p=0.73$), and separate statistical analysis for each gender did not change the statistical conclusions. Moreover, the main effects of group on FA and MD remained significant after a covariate analysis using age, which showed correlations with FA in the patient group.

The results of ANOVAs for right and left hemisphere separately are as follows: $t=0.82$, $p=0.41$ for FA of the right fornix; $t=2.91$, $p=0.005$ for FA of the left fornix; $t=-2.67$, $p=0.009$ for MD of the right fornix; $t=-2.81$, $p=0.006$ for MD of the left fornix. If the Bonferroni-type correction for multiple comparison was employed, the significantly reduced FA of fornix in left hemisphere and significantly increased MD of the fornix in both hemisphere were detected ($p<0.025$).

3.3. Correlations between DTI measures and neuropsychological scores and symptom severity

As for patients with schizophrenia, Spearman's rho showed significant relationships between elevated MD of the left fornix and lower SCR of the verbal learning task (rho$=-0.399$, $p=0.026$) and between elevated MD of the right fornix and poorer performance on the CFT (rho$=-0.468$, $p=0.009$). These correlations were specific to the patient group (Fisher's r to z transformation, $z>2.13$, $p<0.034$) (Fig. 3). Moreover, the correlation between MD of the fornix and SCR of the verbal learning task in the patients with schizophrenia was not specific to the left hemisphere, since the hemispheric difference in the correlations did not reach the statistically significant level (Fisher's r to z transformation, $z=0.42$, $p=0.67$). Similarly, the correlation between MD of the fornix and performance on the CFT in the patients with schizophrenia was not specific to the right hemisphere (Fisher's r to z transformation, $z=0.73$, $p=0.47$).

For the control subjects, none of the correlations between fornix measures and JART score ($-0.092<\text{rho}<0.25$, p's>0.19), verbal memory subscale of the WMS ($-0.18<\text{rho}<-0.004$, p's>0.34), or LFT ($-0.13<\text{rho}<0.26$, p's>0.16) reached the level for statistical significance. Similarly, for the patients with schizophrenia, none of the correlations between fornix measures and JART score ($-0.14<\text{rho}<0.11$, p's>0.47), verbal memory subscale of the WMS ($-0.30<\text{rho}<0.03$, p's>0.11), or LFT ($-0.30<\text{rho}<0.06$, p's>0.10) reached the level for statistical significance.

As for symptoms, none of the correlations between the five factors of the PANSS and DTI measures reached the level for statistical significance.

3.4. Correlations between DTI measures and demographic information

Lower FA of the left fornix in the schizophrenia group showed correlations with increased age (rho$=-0.415$, $p=0.020$), longer duration of illness (rho$=-0.399$, $p=0.036$), and lower class of parental SES (rho$=-0.370$, $p=0.048$), although the correlations did not reach statistical significance after Bonferroni correction. No significant correlation was observed between DTI measures and neuroleptic dosage. In addition, no significant correlation was observed between DTI measures and age, SES, or parental SES in the control subjects.

4. Discussion

The present study demonstrated reduced FA and increased MD in the fornix of patients with schizophrenia compared with matched healthy controls with no significant lateralization. In the patients, increased MD of the fornix further showed significant correlations with lower SCR scores of the verbal learning task and with poorer CFT performance. The correlations were specific to the patient group, as indicated by the significant group difference in the values of these correlations.

The current results from group comparison, both reduced FA and increased MD in the fornix of patients with schizophrenia compared with healthy controls, were consistent with those in a previous study employing ROI methodology in male patients with schizophrenia (Kuroki et al., 2006). In addition, FA reduction of the fornix was consistent with a previous voxel-based analysis study (Kubicki et al., 2005) from the overlapping samples with those in Kuroki et al. (2006). Thus, the present study replicated previous findings, and further extended the observation to both genders.

Various pathological changes can result in both MD increase and FA reduction. One of the putative pathological changes is impairment of axonal myelin sheath. Histological (Hof et al., 2003) and genetic (Hakak et al., 2001) studies indicate the possibility of myelin abnormalities in schizophrenia. However, contribution of myelin abnormalities to MD increase and FA reduction is tentative, because also other pathologies such as brain atrophy can cause both MD increase and FA reduction.

The present study identified worsened memory organization as a functional correlate of the disrupted integrity of the fornix in 31 patients with schizophrenia, while a recent study (Nestor et al., 2007) reported that reduced FA of the fornix correlated with lower scores for general memory in 14 male patients with schizophrenia. Implicit utilization of a strategy such as semantic clustering of encoded words is necessary for better performance on the memory organization task, which presumably recruits functional cooperation between prefrontal cortex and the hippocampus, as well as the hippocampus per se (Bussey et al., 2001; Nohara et al., 2000). Similarly, both prefrontal cortex (Audenaert et al., 2000) and hippocampus (Gleissner and Elger, 2001) are implicated in the performance of CFT, which requires organized word retrieval from the long-term semantic memory system. Thus, it is reasonable to expect that structural abnormality of the fornix, which connects hippocampus and other regions including prefrontal cortex, is associated with dysfunction of memory organization in patients with schizophrenia.

Regarding laterality, a previous study indicated a relationship between the CFT and the right hippocampus (Gleissner and Elger, 2001), and another study showed a relationship between SCR of the verbal learning task and the left prefrontal cortex (Nohara et al., 2000). These two studies are in line with the present correlational findings in terms of laterality. However, the present study could not further discuss the laterality of the findings, since Fisher's r to z transformation did not show significant hemispheric differences in the correlations.

The reason why only MD, not FA, of the fornix correlated with neuropsychological scores is difficult to be interpreted. One possibility is as follows. The white matter of the patients with schizophrenia may include fewer glia cells (Hof et al., 2003), followed by less water content in the white matter, causing MD increase without FA reduction. On the other hand, myelin abnormalities cause both MD increase and FA reduction. Given that patients with schizophrenia have both of these histological changes (fewer glia cells and myelin abnormalities), both MD increase and FA reduction are observed. Presumably, having fewer glia cells in the fornix is more strongly implicated in dysfunction of memory organization than having myelin abnormalities. However, it is not totally ruled out that the correlation with only MD reflects an increase of CSF space in schizophrenia through partial volume effect, although an increase of CSF is likely to be associated with FA reduction as well as MD increase.

The current study also showed correlations between reduced FA and increased age and between reduced FA and duration of illness in patients with schizophrenia although the significance levels were marginal. These correlations might indicate that illness progression affects deterioration of FA in the fornix of patients with schizophrenia. On the other hand, fornix MD correlated with cognitive function, which is comparatively unaltered throughout the duration of the disease (Rund, 1998), while MD did not correlate with either age or duration. Therefore, it is possible that fornix FA represents some aspect of progressive pathophysiology and fornix MD represents some aspect of stable pathophysiology of schizophrenia. This notion is supported by our previous study reporting that reduced FA was more strongly correlated with increased age in the frontotemporal white matter, compared with volume and MD (Abe et al., 2008). On the other hand, Kuroki et al. (2006) reported that age correlated positively with MD of the fornix for a healthy control group and age did not correlate with either FA or MD for a schizophrenia group. Inconsistency in the relationship between age and DTI measures of the fornix may partially derive from cross-sectional designs, thus, it will be important in future studies to employ longitudinal designs.

The present study has several limitations. First, although coronal sections are more suitable for seed-sphere placement in the fornix, we used axial sections for seed-sphere placement because DTI scans were acquired as axial slices. Second, the voxel size was not small enough relative to the size of the fornix. The comparatively large voxel size caused partial volume effect, resulting in relatively low FA values of the fornix. In addition, we had to adopt a low cut-off point ($FA > 0.18$) in tractography because tractography was otherwise difficult to be completed, which may be another cause of low FA values of the fornix. Third, the correlation with memory organization may not be specific to the fornix because we did not compare the fornix with any control region. Fourth, all the patients were taking antipsychotic medications. The medication might influence DTI measures, although neuroleptic dosage did not correlate with DTI measures in the present study. Thus, it will be important in future studies to examine integrity of the fornix in unmedicated patients with schizophrenia.

In conclusion, the current DTI study suggests that disrupted integrity of the fornix contributes to core cognitive deficits, specifically impairment of memory organization and the semantic memory system in patients with schizophrenia.

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Contributors

Authors Yamasue and Kasai designed the study and wrote the protocol. Author Takei managed the DTI measurement and the statistical analyses. Authors Abe, Yamada, Inoue, Suga, Sekita, Sasaki, and Aoki recruited the subjects, took MRI, and performed clinical evaluation. Authors Takei, Yamasue, Kasai and Rogers wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Kunio Takei, Hidenori Yamasue, Osamu Abe, Haruyasu Yamada, Hideyuki Inoue, Motomu Suga, Kayoko Sekita, Hiroki Sasaki, Mark Rogers, Shigeki Aoki, and Kiyoto Kasai declare that they have no conflicts of interest.

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Letter to the Editor

Current state of refusal to attend school in Japan

AN INCREASE IN the number of students refusing to attend school has been reported as a major social problem in Japan.[1] The Ministry of Education, Culture, Sports, Science and Technology established a school counselor system in 1995 and started a conference of investigation research cooperators regarding refusal to attend school in September 2002. In March 2003 the Ministry reported the current state of the problem and provided a list of preventive measures to use in the school, home, and local community. Because it is important to examine the effect of the measures, we studied the number of students refusing to attend school among all the elementary and junior high schools in Japan from databases without individual information made available by the Ministry of Education, Culture, Sports, Science and Technology[2] during 1995–2006. The Ministry of Education, Culture, Sports, Science and Technology defines refusal to attend school as lack of attendance by students, who cannot do so for psychological, emotional, physical or social reasons, and who were absent from school for more than 30 days per year for reasons other than sickness or economic causes.

In the study period the number of students refusing to attend school increased from 81 591 (1995) to 138 722 (2001), and the levels were then maintained at around 120 000 or 130 000: 131 252 (2002), 126 226 (2003), 123 358 (2004), 122 287 (2005), and 126 764 (2006), in contrast to the gradual decrease in the number of total students from 12 940 636 (1995) to 10 788 944 (2006). The proportion of students refusing to attend school compared to the total number of students similarly increased from 0.63% (1995) to 1.23% (2001), and the levels were then sustained at around 1.13–1.18%: 1.18% (2002), 1.15% (2003), 1.14% (2004), 1.13% (2005), and 1.17% (2006). Therefore, the previous clear increase in the rate of students refusing to attend school ceased after 2002. This may suggest the effectiveness of the measures by the Ministry of Education, Culture, Sports, Science and Technology. We consider that the Ministry's measures with regard to school refusals were effective based on the increase in the number of schools where the school counselors were posted. The number of such schools will increase in the future in Japan, and improvement in the quality of school counselors is thought to contribute to the decrease in the number of school refusals. To further decrease the number of absentees, we conclude that cooperation is needed among the schools, the board of education, the school counselors, families, communities, medical institutions, and school administrators.

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Behavioral/Systems/Cognitive

Differential Contributions of Prefrontal and Hippocampal Dopamine D_1 and D_2 Receptors in Human Cognitive Functions

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Dopamine D_1 receptors in the prefrontal cortex (PFC) are important for prefrontal functions, and it is suggested that stimulation of prefrontal D_1 receptors induces an inverted U-shaped response, such that too little or too much D_1 receptor stimulation impairs prefrontal functions. Less is known of the role of D_2 receptors in cognition, but previous studies showed that D_2 receptors in the hippocampus (HPC) might play some roles via HPC–PFC interactions. We measured both D_1 and D_2 receptors in PFC and HPC using positron emission tomography in healthy subjects, with the aim of elucidating how regional D_1 and D_2 receptors are differentially involved in frontal lobe functions and memory. We found an inverted U-shaped relation between prefrontal D_1 receptor binding and Wisconsin Card Sorting Test performance. However, prefrontal D_2 binding has no relation with any neuropsychological measures. Hippocampal D_2 receptor binding showed positive linear correlations not only with memory function but also with frontal lobe functions, but hippocampal D_1 receptor binding had no association with any memory and prefrontal functions. Hippocampal D_2 receptors seem to contribute to local hippocampal functions (long-term memory) and to modulation of brain functions outside HPC ("frontal lobe functions"), which are mainly subserved by PFC, via the HPC–PFC pathway. Our findings suggest that orchestration of prefrontal D_1 receptors and hippocampal D_2 receptors might be necessary for human executive function including working memory.

Key words: dopamine; D_1 receptors; D_2 receptors; prefrontal cortex; hippocampus; positron emission tomography

Introduction

Because dopamine D_1 receptors in the prefrontal cortex (PFC) are several times more abundant than D_2 receptors (Hall et al., 1994), the relationship between D_1 receptors and PFC functions have been widely investigated. Sawaguchi and Goldman-Rakic (1994) demonstrated that local administration of D_1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate. In human, Müller et al. (1998) reported that systemic administration of a mixed D_1/D_2 agonist facilitated working memory, whereas the selective D_2 agonist had no effect, indicating that the dopaminergic modulation of working memory processes is mediated primarily via D_1 receptors. The use of positron emission tomography (PET) allows us to quantify dopamine receptors *in vivo*, and previous studies reported that altered prefrontal D_1 receptors in schizophrenia were associated with working memory deficits (Okubo et al., 1997; Abi-Dargham et al., 2002).

In contrast to D_1 receptors, relatively less attention has been paid to the role of prefrontal D_2 receptors in cognitive functions. It was reported that blockade of D_2 receptors in PFC did not impair working memory in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994), but some human studies reported that systemic administration of D_2 agonist or antagonist modulated cognitive functions that are subserved by the prefrontal cortex (McDowell et al., 1998; Mehta et al., 1999). Because the density of D_2 receptors in extrastriatal regions is very low (Suhara et al., 1999), PET studies investigating the involvement of extrastriatal D_2 receptors in cognition have been limited. With the introduction of high-affinity PET radioligands such as [^{11}C]FLB457, it has become possible to quantify extrastriatal D_2 receptors by PET (Halldin et al., 1995). Using [^{11}C]FLB457, Kemppainen et al. (2003) reported that a reduction of D_2 receptors in the hippocampus (HPC) in Alzheimer's disease patients was correlated with memory impairments. Our recent PET study also showed that D_2 receptors in HPC were associated not only with memory function but also with frontal lobe functions (Takahashi et al., 2007), suggesting dopaminergic modulation on HPC–PFC inter-

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actions during the cognitive process (Laroche et al., 2000; Thierry et al., 2000; Goto and Grace, 2008).

In this study, we measured both D_1 and D_2 receptors in PFC and HPC using PET in normal healthy subjects, and aimed to elucidate how regional D_1 and D_2 receptors are differentially involved in neurocognitive performance including memory and frontal lobe functions. A body of animal studies has indicated that stimulation of D_1 receptors in PFC produces an inverted U-shaped dose–response curve, such that too little or too much D_1 receptor stimulation impairs PFC functions (Goldman-Rakic et al., 2000; Williams and Castner, 2006; Vijayraghavan et al., 2007). We hypothesized that prefrontal D_1 receptors would be more related to frontal lobe functions than prefrontal D_2 receptors, and that, specifically, an inverted U-shaped relation between prefrontal D_1 receptor binding and prefrontal functions would be observed in the normal physiological condition in healthy volunteers. In addition, we predicted that D_2 receptors in HPC would be more related to memory than D_1 receptors in HPC.

Materials and Methods

Subjects. Twenty-three healthy male volunteers [mean age 25.7 ± (SD) 4.3 years] were studied. Seven of the 23 subjects had participated in our earlier study (Takahashi et al., 2007). They did not meet the criteria for any psychiatric disorder based on unstructured psychiatric screening interviews. None of the controls were using alcohol at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. All subjects were right-handed according to the Edinburgh Handedness Inventory. All subjects underwent magnetic resonance imaging (MRI) to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all subjects, and the study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba Japan.

PET scanning. PET studies were performed on ECAT EXACT HR+ (CTI; Siemens). The system provides 63 planes and a 15.5 cm field of view. To minimize head movement, a head fixation device (Fixster) was used. A transmission scan for attenuation correction was performed using a germanium 68–gallium 68 source. Acquisitions were done in three-dimensional mode with the interplane septa retracted. For evaluation of D_1 receptors, a bolus of 213.9 ± 20.5 MBq of [^{11}C]SCH23390 with specific radioactivities (52.1 ± 28.9 GBq/μmol) was injected intravenously from the antecubital vein with a 20 ml saline flush. For evaluation of extrastriatal D_2 receptors, a bolus of 215.4 ± 24.5 MBq of [^{11}C]FLB457 with high specific radioactivities (171.0 ± 58.0 GBq/μmol) was injected in the same way. The mean injected amounts of [^{11}C]SCH23390 and [^{11}C]FLB457 were 1.18 ± 0.20 μg and 0.47 ± 0.17 μg, respectively. Dynamic scans were performed for 60 min for [^{11}C]SCH23390 and 90 min for [^{11}C]FLB 457 immediately after the injection. All emission scans were reconstructed with a Hanning filter cutoff frequency of 0.4 (full width at half maximum, 7.5 mm). MRI was performed on Gyroscan NT (Philips Medical Systems) (1.5 T). T1-weighted images of the brain were obtained for all subjects. The scan parameters were 1-mm-thick, three-dimensional T1 images with a transverse plane (repetition time/echo time, 19/10 milliseconds; flip angle, 30°; scan matrix, 256 × 256 pixels; field of view, 256 × 256 mm; number of excitations, 1).

Quantification of D_1 and D_2 receptors in PFC and HPC. The tissue concentrations of the radioactivities of [^{11}C]SCH23390 and [^{11}C]FLB457 were obtained from regions of interest (ROIs) defined on the PET images of summated activity for 60 and 90 min, respectively, with reference to the individual MRIs that were coregistered on summated PET images and the brain atlas. The regions were PFC, HPC and cerebellar cortex. Each ROI consisted of three axial slices. ROI of PFC occupies the middle third of the middle frontal gyrus and the rostral portion of the inferior frontal gyrus (approximately corresponding to the dorsolateral prefrontal cortex or Brodmann area 46). ROI of HPC was set at the level of the midbrain. The anterior boundary was identified at the level of the inferior horn of the lateral ventricle. The posterior boundary was identified at the level of the collateral sulcus. Although [^{11}C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated because the duration of the [^{11}C]FLB457 PET study was not sufficient to obtain equilibrium in the striatum (Olsson et al., 1999; Suhara et al., 1999). Quantitative analysis was performed using the three-parameter simplified reference tissue model (Lammertsma and Hume, 1996). The cerebellum was used as reference region because it has been shown to be almost devoid of D_1 and D_2 receptors (Farde et al., 1987; Olsson et al., 1999; Suhara et al., 1999). The model provides an estimation of the binding potential ($BP_{ND\ (nondisplaceable)}$) (Innis et al., 2007), which is defined by the following equation: $BP_{ND} = k3/k4 = f2\ Bmax/\{Kd\ [1 + \sum i\ Fi/Kdi]\}$, where k3 and k4 describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, f2 is the "free fraction" of nonspecifically bound radioligand in brain, Bmax is the receptor density, Kd is the equilibrium dissociation constant for the radioligand, and Fi and Kdi are the free concentration and the dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996).

Neuropsychological tests. A battery of cognitive tests was given by an experienced clinical neuropsychologist. The neuropsychological tests used were Rey's Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth's Complex Figure Test (ROCFT), Keio version of the Wisconsin Card Sorting Test (WCST) (Igarashi et al., 2002), Verbal Fluency Test, and Raven's Colored Progressive Matrices (RCPM). RAVLT is used to evaluate the performance of verbal memory, and ROCFT is used as a measure of nonverbal visual memory. RAVLT and ROCFT were performed in the standard manner (Lezak, 1995). In RAVLT, 15 words were presented auditorily in the same sequence in five trials, ending with a free recall of the words (immediate recall). After the five trials, an interference list was presented and recalled, and then the subjects were instructed to recall the first list of words (delayed recall). In ROCFT, after the copy trial, subjects were asked to reproduce a figure from memory (immediate recall). After a 15 min pause, the subjects were asked to reproduce the figure from memory again (delayed recall). WCST is a test for executive function or cognitive flexibility involving working memory (Berman et al., 1995). It has been shown to be sensitive to dysfunction of PFC (Nelson, 1976). In WCST, categories achieved (CA), total errors (TE) and perseverative errors of Nelson (PE) were evaluated (Lezak, 1995). In the phonemic verbal fluency test, the subject was requested to retrieve in 1 min as many words as possible beginning with the Japanese syllabic characters (hiragana) "shi," "i" and "re," respectively. In the semantic verbal fluency test, the subject was requested to recall in 1 min as many words as possible belonging to a given semantic category (e.g., animals, fruit) (Lezak, 1995). RCPM was used as a general visuospatial intelligence test.

Statistical analyses. Although the selection of subjects was confined to young males in their 20's and 30's, the possible age effect on the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457, and neuropsychological performance were examined using Pearson correlation analysis. To explore the relation between D_1 and D_2 receptors and cognitive functions, linear regression between the BP_{ND} values of each ROI and each neuropsychological performance was analyzed, and the threshold for significance was set at $p = 0.05/2 = 0.025$ to correct for two regions (PFC and HPC). Although a single dominant factor underlying the scores on all tests, i.e., general cognitive ability, might contribute to intercorrelations across the tests, what we measure with neuropsychological tests is, by nature, a dimensionality of cognitive ability. Therefore, correction of p values for multiple comparisons was done only for regions, not for multiple neuropsychological tests. To examine putative nonlinear (inverted U-shaped) relations between prefrontal dopamine receptors and frontal lobe functions, quadratic regression between the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and neuropsychological performance was analyzed by SPSS package (SPSS).

To confirm the findings of the ROI analysis, parametric images of BP_{ND} (Gunn et al., 1997) were analyzed using statistical parametric mapping software (SPM2) (Wellcome Department of Imaging, Institute of Neurology, University College of London, London, UK). Normalized BP_{ND} images were smoothed with a Gaussian filter to 16 mm full-width

Table 1. Mean scores of neuropsychological tests and linear relations between and neuropsychological measures and BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in the prefrontal cortex and hippocampus

Neuropsychological tests	Mean scores	Prefrontal cortex r (p)		Hippocampus r (p)	
		[^{11}C]SCH23390	[^{11}C]FLB457	[^{11}C]SCH23390	[^{11}C]FLB457
RALVT immediate	57.3 ± 6.2	0.07 (0.74)	0.16 (0.47)	0.10 (0.66)	0.37 (0.09)
RALVT delayed	13.0 ± 1.5	0.14 (0.53)	0.02 (0.94)	0.08 (0.72)	0.28 (0.20)
ROCFT immediate	27.7 ± 3.9	0.11 (0.63)	0.31 (0.15)	0.21 (0.34)	0.73 (p<0.001)**
ROCFT delayed	27.3 ± 4.8	0.12 (0.58)	0.38 (0.07)	0.11 (0.60)	0.67 (p<0.001)**
WCST CA	5.4 ± 1.2	0.42 (0.049)*	0.03 (0.89)	0.21 (0.33)	0.30 (0.17)
WCST TE	11.3 ± 3.7	−0.41 (0.049)*	−0.15 (0.51)	−0.30 (0.16)	−0.51 (0.01)**
WCST PE	0.8 ± 1.4	−0.27 (0.21)	−0.18 (0.42)	−0.31 (0.15)	−0.59 (0.003)**
Phonemic verbal fluency	30.9 ± 9.3	0.21 (0.35)	0.21 (0.34)	0.20 (0.36)	0.47 (0.02)**
Semantic verbal fluency	46.1 ± 7.9	−0.07 (0.76)	0.09 (0.69)	0.06 (0.77)	0.17 (0.45)
RCPM (sec)	188.5 ± 36.0	0.10 (0.65)	−0.04 (0.87)	0.11 (0.64)	0.08 (0.70)

*$p < 0.05$. **Significant after correction for multiple statistical tests (new significance threshold: $p < 0.025$[0.05/2]).

half-maximum. Using each individual cognitive performance as covariate, regression analyses with the BP_{ND} images and the covariates were performed.

Results

The mean [^{11}C]SCH23390 BP_{ND} values of PFC and HPC were 0.41 ± 0.06 (range: 0.29–0.59) and 0.33 ± 0.09 (range: 0.20–0.53), respectively. The mean [^{11}C]FLB457 BP_{ND} values of PFC and HPC were 1.16 ± 0.21 (range: 0.82–1.58) and 1.57 ± 0.28 (range: 0.98–1.92), respectively. The mean scores of the neuropsychological data are shown in Table 1. There was no age effect on the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in the two ROIs, nor on any neuropsychological performance ($p > 0.01$).

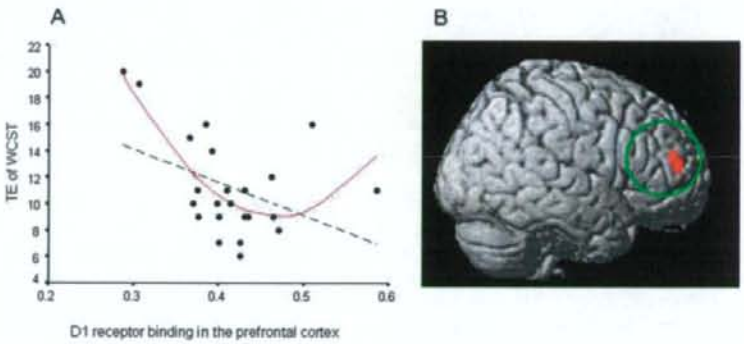

Figure 1. Quadratic (inverted U-shaped) relation between D_1 receptor binding in PFC and performance of WCST. ***A***, ROI analysis revealed a significant quadratic regression between the BP_{ND} value of [^{11}C]SCH23390 in PFC ($BP_{D1\ PFC}$) and TE of WCST. Red solid line, quadratic regression; black broken line, linear regression. Based on ROI analysis, the relation between $BP_{D1\ PFC}$ and TE can be expressed as follows: $TE = 326.92(BP_{D1\ PFC} - 0.47)^2 + 9.10$. ***B***, Using this equation, SPM analysis also revealed a significant quadratic regression between prefrontal D_1 receptor binding and TE of WCST ($p < 0.001$, uncorrected, extent threshold >30 voxels).

Quadratic regression analysis revealed a significant "U-shaped" relation between the BP_{ND} value of [^{11}C]SCH23390 in PFC and TE of WCST ($p < 0.001$, $r = 0.72$). (Because TE of WCST is a negative measure of frontal lobe function, the relation is not "inverted") (Fig. 1). The BP_{ND} value of [^{11}C]SCH23390 in PFC and CA of WCST also showed significant quadratic (inverted U-shaped) relation ($p < 0.001$, $r = 0.78$). However, no quadratic relation was found between the BP_{ND} value of [^{11}C]FLB 457 in PFC and any neuropsychological measures. The linear relations between neuropsychological measures and the BP_{ND} value of each ROI are shown in Table 1. As for D_1 receptors, the BP_{ND} value of [^{11}C]SCH23390 in PFC was positively correlated with CA of WCST ($p = 0.049$, $r = 0.42$), and negatively correlated with TE of WCST ($p = 0.049$, $r = -0.41$) although these relations did not survive a threshold corrected for multiple comparisons. The BP_{ND} value of [^{11}C]SCH23390 in HPC was not correlated with any neuropsychological measures. With regard to D_2 receptors, the BP_{ND} value of [^{11}C]FLB457 in HPC was positively correlated with immediate and delayed recall scores of ROCFT and phonemic verbal fluency, and negatively correlated with CA and TE of WCST. The BP_{ND} value of [^{11}C]FLB457 in PFC was not correlated with any neuropsychological measures. Figure 2 shows these relationships.

D_1 binding in PFC showed significant correlation with D_1 binding in HPC ($r = 0.74$, $p < 0.001$) and trend level correlation with D_2 binding in PFC ($r = 0.41$, $p = 0.05$), but no correlation with D_2 binding in HPC ($r = 0.27$, $p = 0.22$). D_2 binding in HPC showed significant correlation with D_2 binding in PFC ($r = 0.50$, $p = 0.02$) and trend level correlation with D_1 binding in HPC ($r = 0.36$, $p = 0.09$). D_2 binding in PFC showed no correlation with D_1 binding in HPC.

Using SPM2, we conduced standard voxel-based morphometry without modulation (Ashburner and Friston, 2000) to test whether the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and HPC were related to the prefrontal and hippocampal gray matter concentration in the normalized images, respectively. The age and total gray matter (GM) volume were treated as confounding covariates in an analysis of covariance. The total GM volume was given by the total number of voxels within the GM compartment of each subject. The analysis revealed that there were no significant correlations between the BP values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and HPC and the concentration of gray matter in the prefrontal and hippocampal regions, respectively, at a threshold of $p = 0.01$, uncorrected.

Discussion

Although D_1 receptor binding in PFC showed trend-level positive linear correlations with WCST performance, quadratic regression analysis revealed significant inverted U-shaped relations between D_1 receptors in PFC and WCST performance. That is, a too high or too low level of D_1 receptor expression in PFC leads to high errors and a low number of categories achieved. However, D_2 receptor binding in PFC did not show significant relation with

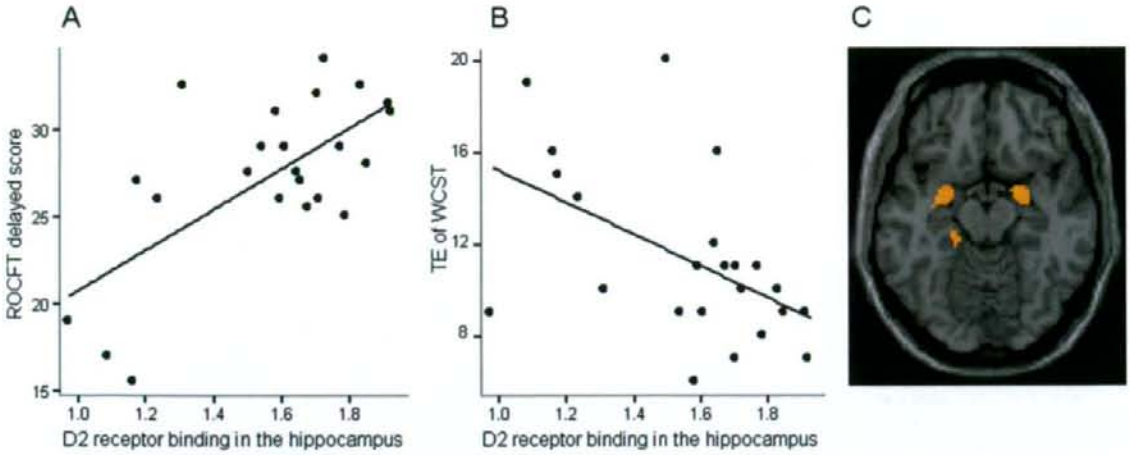

Figure 2. Correlations between D_2 receptor binding in the hippocampus and memory. ***A***, ***B***, Significant positive linear correlations between the BP_{ND} value of [^{11}C]FLB457 in the hippocampus and the delayed recall score of ROCFT and (***B***) TE of WCST revealed by ROI analysis. ***C***, The SPM result of a positive linear correlation between hippocampal D_2 receptor binding and the delayed recall score of ROCFT is shown ($p < 0.005$, uncorrected, extent threshold >30 voxels).

any neuropsychological measures. With regard to dopamine receptors in HPC, D_2 receptor binding in HPC showed positive liner correlations not only with memory function but also with frontal lobe functions, whereas D_1 receptor binding in HPC did not show significant relation with any neuropsychological measures. WCST involves a set-shifting component as well as a working memory component, although the two abilities are not mutually exclusive (Konishi et al., 1999). Working memory requires the active maintenance and manipulation of trial-unique information in a short-term memory buffer (Goldman-Rakic, 1995; Fuster, 2000). Thus, set-shifting could be regarded as updating of working memory content, and it has been demonstrated that updating of working memory content and shifting of cognitive set have a similar cognitive aspect in common (Konishi et al., 1998). Thus, in normal human subjects, the individual difference of working memory capacity could contribute to the difference in the performance of tests for cognitive flexibility.

Previous animal studies demonstrated that local injection of D_1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994). In a human study, systemic administration of a mixed D_1/D_2 agonist, pergolide, facilitated working memory, but the selective D_2 agonist bromocriptine had no effect, indicating that the dopaminergic modulation of working memory is mediated primarily via stimulation of D_1 receptors (Müller et al., 1998). Subsequent animal studies indicated that stimulation of D_1 receptors in PFC produces an inverted U-shaped response in working memory, with the response being optimized within a narrow range of D_1 receptor stimulation (Goldman-Rakic et al., 2000; Lidow et al., 2003; Castner and Goldman-Rakic, 2004; Seamans and Yang, 2004; Vijayraghavan et al., 2007). Recent human studies have investigated the effect of a functional polymorphism in the catechol *O*-methyltransferase gene, which has been shown to modulate the prefrontal dopamine level, on prefrontal function. The results also suggested that dopamine transmission in PFC produces an inverted U-shaped response, meaning that too little or too much dopamine signaling would impair prefrontal functions, although these studies could not identify the receptor subtype that plays a central role in this effect (Mattay et al., 2003; Williams-Gray et al., 2007).

Our PET finding is the first direct evidence in human that demonstrated an inverted U-shaped relation between D_1 receptors in PFC and executive function including working memory in normal healthy subjects. Our previous PET study revealed that, compared with normal controls, D_1 receptors in PFC were decreased in schizophrenia, which was associated with poor performance on WCST (Okubo et al., 1997). However, another PET study reported that an increase in D_1 receptors in PFC was associated with working memory deficits in schizophrenia (Abi-Dargham et al., 2002). It has been discussed that these inconsistent results might stem from several factors including differences in radioligands and patient demographics. Although the reasons for these inconsistent results need to be clarified in the future, an inverted U-shaped response can account for working memory deficits in schizophrenia whether D_1 receptors in PFC are increased or decreased in patients, because the D_1 receptor inverted U-shaped response is observed within a narrow range of the normal physiological condition (Williams and Castner, 2006; Vijayraghavan et al., 2007). An inverted U-shaped response has been suggested based on cognitive and behavioral studies, but the exact physiological mechanism of this effect has not yet been fully understood. A recent monkey electrophysiology study has demonstrated a neuron-level mechanism that constitutes the inverted U-shaped response whereby too much or too little stimulation of prefrontal D_1 receptors leads to working memory deficits. D_1 receptor stimulation had a suppressive effect on the PFC neural activities involved in a spatial working memory task. Moderate D_1 receptor stimulation spatially tunes PFC neurons that process target signals by preferentially suppressing nontarget (noisy) neural activities, whereas excessive D_1 receptor stimulation induces nonselective suppression of PFC neural activities regardless of whether the neural activities are task-related or not (Vijayraghavan et al., 2007).

Animal studies have suggested that the inverted U-shaped principle of D_1 receptor stimulation mediating working memory does not necessarily apply to other prefrontal functions (Floresco and Magyar, 2006). Therefore, it is noteworthy that prefrontal D_1 receptors were not associated with other prefrontal measures besides WCST, because fluency task by phonetic or semantic cues

and problem-solving test with visuospatial analysis are less dependent on the working memory process.

Considering that D_1 binding in PFC was not correlated significantly with D_2 binding either in PFC or HPC, D_1- and D_2-mediated working memory processes are considered to contribute differently to the completion of WCST. Although previous animal studies showed that working memory or executive function mainly depends on D_1 receptors, not on D_2 receptors in PFC (Sawaguchi and Goldman-Rakic, 1994; Seamans et al., 1998), a recent rat study demonstrated that D_2 receptors in PFC were necessary for set-shifting ability (Floresco et al., 2006). It has been suggested that when the dopamine level is high under a novel circumstance, the prefrontal network is mainly modulated by D_2 receptors. In such state, the network is likely to process multiple information (Seamans and Yang, 2004; Floresco et al., 2006). During the set-shifting stage of WCST, one needs to disengage from the previous strategy and compare alternative options under a new condition. After shifting attentional sets, one needs to learn and maintain a new strategy of WCST. In such condition, the dopamine level is considered to be moderate and D_1 receptors play a central role in stabilizing the network (Seamans and Yang, 2004; Floresco et al., 2006). We did not find any correlation between D_2 binding in PFC and WCST performances, possibly attributable to the fact that the working memory component and the set-shifting component are not entirely dissociable in WCST (Konishi et al., 1999). Instead, D_2 binding in HPC was related to WCST performances. Although the role of hippocampal D_2 receptors in set-shifting is not known, a possible interpretation is that in the initial set-shifting stage of WCST, D_2 receptors in HPC might play a role in quick learning and comparison to guide future behaviors, and once a new strategy is learned, D_1 receptors in PFC might contribute to the stability and maintenance of the novel strategy.

The association between hippocampal D_2 receptors and memory is consistent with the findings of previous PET studies (Kemppainen et al., 2003; Takahashi et al., 2007). The finding that hippocampal D_2 binding was more related to visuospatial memory than to verbal memory might stem from the fact that verbal learning is dependent on regions other than HPC, such as anterior, lateral and superior temporal lobes, which are involved in human language, although HPC plays a central role in both types of memory (Hodges and Graham, 2001). Umegaki et al. (2001) reported that injection of a D_2 receptor antagonist into HPC impaired memory performance and that the memory impairment was ameliorated by coinjection of a D_2 receptor agonist. They also found that local infusion of D_2 agonist into HPC stimulated acetylcholine release in HPC and ameliorated scopolamine-induced memory impairment (Fujishiro et al., 2005). In addition, hippocampal D_2 receptors appear to be involved in synaptic plasticity. It has been reported that D_2 antagonist inhibited long-term potentiation in HPC (Frey et al., 1990; Manahan-Vaughan and Kulla, 2003), the key mechanism underlying memory consolidation (Jay, 2003; Lynch, 2004). There is some evidence from animal studies that hippocampal D_1 receptors are also involved in memory (Hersi et al., 1995a,b; Bach et al., 1999), but supporting our PET data, Wilkerson and Levin (1999) reported that hippocampal D_1 receptors were not as responsible as D_2 receptors for memory functions.

In line with our previous study (Takahashi et al., 2007), we also found hippocampal D_2 receptors to be involved in the performance of WCST and phonemic verbal fluency, which is more dependent on PFC than semantic verbal fluency. Patients with lesions in HPC sometimes show deficits in WCST (Corkin, 2001; Igarashi et al., 2002). These observations suggest that hippocampal D_2 receptors could modulate PFC activity by the HPC–PFC pathway, which plays a significant role in the cognitive process (Laroche et al., 2000; Thierry et al., 2000). Accumulating evidence has suggested the modulatory effects of dopamine on HPC–PFC interactions (Seamans et al., 1998; Aalto et al., 2005; Tseng et al., 2007; Goto and Grace, 2008). Conceivably, dopamine influences PFC neurons directly by prefrontal D_1 receptors and indirectly by hippocampal D_2 receptors via the HPC–PFC pathway.

Müller et al. (1998) reported that the systemic administration of the mixed D_1/D_2 agonist pergolide facilitated working memory, whereas selective D_2 agonist had no effect. However, there is converging evidence from human and animal studies to suggest the involvement of D_2 receptors in cognitive functions. It was reported that the systemic administration of D_2 agonist in human improved cognitive functions including working memory and executive functions (McDowell et al., 1998), and the administration of D_2 antagonist impaired those functions (Mehta et al., 1999). In an animal study, it was reported that mice lacking D_2 receptors showed a working memory deficit (Glickstein et al., 2002). These studies, however, did not reveal the regions most responsible for these effects. Moreover, although the involvement of D_1 receptors in working memory is widely recognized, it was not clear whether D_1 receptor stimulation alone or the combination of D_1 and D_2 receptor stimulation is most effective. Our finding suggested that orchestration of prefrontal D_1 receptors and hippocampal D_2 receptors might be necessary for executive functions including working memory.

The current study has several limitations. First, although BP_{ND} is the complex value of receptor density and affinity (the inverse of Kd), previous studies indicated that the affinity does not differ according to region (Suhara et al., 1999) and that extrastriatal binding of current PET ligands is not sensitive to endogenous dopamine (Abi-Dargham et al., 1999; Okauchi et al., 2001). Still, we should keep in mind that the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 might not necessarily be equivalents for D_1 and D_2 receptor functions, respectively. This emphasizes the need for PET investigations of the relation of BP_{ND} and presynaptic function or second messenger beyond dopamine receptors. Alternatively, multimodal imaging study combining the current method with other modalities such as functional MRI might also be advantageous in investigating the direct relation between dopamine receptor function and PFC functions. Second, we measured the level of dopamine receptor binding during a resting state rather than during cognitive tasks. It is difficult to measure endogenous dopamine release in extrastriatal regions with the current PET ligands (Abi-Dargham et al., 1999; Okauchi et al., 2001). Future study with radioligands more sensitive to endogenous dopamine release will enable us to examine its degree of receptor occupancy. Finally, attributable to limitations of the [^{11}C] radioligand, the data of [^{11}C] FLB457 binding in the striatum was not available. The striatum plays an important role in the prefrontal-hippocampus pathway. PET data in the striatum would lead to a better understanding of the interaction of these three regions. Future study with triple radioligands such as [^{11}C]SCH23390, [^{11}C] FLB457 and [^{11}C] raclopride will enable us to examine striatal and extrastriatal D_1 and D_2 receptors in the same subject.

In summary, we found that an inverted U-shaped relation existed between D_1 receptor binding in PFC and WCST performance, indicating an inverted U-shaped relation between prefrontal D_1 receptors and working memory, and that prefrontal D_2 receptor binding was not related to any frontal lobe functions.

Hippocampal D_2 receptors seem to contribute to local hippocampal functions (long-term memory) and to modulation of brain functions outside HPC (frontal lobe functions), which are mainly subserved by PFC, via the HPC–PFC pathway. Our findings suggest that prefrontal D_1 receptors and hippocampal D_2 receptors might be targets for pharmacological therapeutics for cognitive and memory impairments observed in neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease and schizophrenia.

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4. 前駆期における非生物学的治療

はじめに

前駆期は，確定診断に至るほどの症状が出そろう前の，前ぶれの症状が出現している時期であるが，この時期を厳密に定義することは難しい．前駆期の概念についての論考は別項に譲ることとし，ここでは統合失調症を含めた精神病に移行するリスクが高い精神状態である発症危険精神状態（at risk mental state：ARMS）[1] *1 の非生物学的治療について述べたい．

ARMS に対する治療

ARMS の患者は，精神病的な症状を示しつつも精神病には至っていないという二律背反的な特徴があり，治療者は精神病を前提とした治療を行うべきか否かという判断に迫られることがしばしばであろう．現時点では，ARMS に対する介入法についてのエビデンスは確立されていないが，ARMS の概念が国際的に普及するとともに，世界各国から介入方法についての研究が報告され，その経験が蓄積されつつある．

ARMS への介入は，現れている症状に対する治療と将来の精神病や統合失調症に対する予防という大きく分けて 2 つの目的がある[2]．ARMS では，微弱な陽性症状が一般に認められるが，一方で，気分障害や不安障害などが“併存”することも知られており，その表出は異種的である．また，精神病への移行率は，治療的な介入を行った場合には最初の数年でおおむね 10 ～ 40 %の範囲にあり，経過もさまざまである*2．したがって，ARMS の患者に対して最適な治療指針を決定するためには，鑑別診断と縦断的フォローアップの複雑さについて認識したうえで，詳細なアセスメントに依拠した治療を行う必要性がことさら高く，個別的な治療戦略が重要となる．

統合失調症の前駆期は思春期に始まることがしばしばであり，ARMS と診断される若者の多くも成長中の発達課題を抱えている．思春期心性や青年期の正常な心理過程が，問題となっている症状に反映されることも多く，これを理解することが適切な病態把握や心理的介入の手助けとなる．顕在発症後の精神病と比較すると短期的な予後は良好であり，現実に基づいた楽観的で回復に焦点をあてた治療姿勢が重要である[6]．若者特有の自

＊1
ARMS では，統合失調症の前駆期にある若者が多く含まれるが，必ずしもすべてが統合失調症の前駆期にあるわけではなく，統合失調症の前駆期とは相同でない．ただし，臨床的に統合失調症の前駆期を疑う症例の多くが含まれることも確かである．

＊2
薬物療法や認知行動療法（cognitive behavioural therapy：CBT）などの特別な介入を行った場合と行わない場合とを比較したこれまでの無作為化対照試験の結果では，特別な介入群 vs. 対照群における短期間の精神病移行率は，10 % vs. 36 %，16 % vs. 38 %，6 % vs. 26 %と，いずれも特別な介入を行ったほうが，精神病の移行率は低くなっている[1,3,4]．
また，メルボルンの PACE（Personal Assessment and Crisis Evaluation）クリニックによる調査では，サービスの開始初期の 1995 年からサービスの発展した 2000 年までの 6 年間で，精神病の移行率が 50 %から 12 %にまで低下した[5]．初期に比べて，より軽症の患者が早期に発見され，治療効果が上がっている可能性が指摘されている．

立心や興味関心などを引き出しながら，治療に生かすことが役立つ．

治療の構成要素

ケース・マネジメント

ARMS の患者は，日常生活上の現実的な問題に困難を抱えていることがしばしばであり，より実際的な問題での支援（たとえば，学校や職場への説明や調整，休職や休学の手続き，進路の選択，就労の相談，自立支援医療の申請など）が必要となる．問題となっている精神病性の症状そのものよりも，このような実際的な問題のほうが患者にとってはより切実な場合も多い．日常生活の基本的な部分の問題が解決されていない状況は，心理療法や薬物療法を含めたあらゆる介入の効果に影響を及ぼす．ケース・マネジメントは，後に述べる治療関係づくりや問題指向的アプローチにおいても重要視される，治療の基本的な要素である．

心理教育

ARMS に対してどのような情報を伝えるべきかは議論のあるところである．予防的な介入の意義を伝えるためには，予防介入を行わない場合にどのようなリスクがあるのかを伝える必要があるが，一方で，精神病や統合失調症の負の部分を過度に強調することは，精神病や統合失調症に対するスティグマを強める危険性を伴う．精神病が重大な問題であることを伝える一方で，予後は良好な場合も含めてさまざまであること，効果的な治療が利用できること，精神病になった場合にはそうした治療がすぐに受けられるという情報も同時に伝える必要がある[2]．

発病のリスク，精神病，統合失調症などの用語の使用については，十分な検討が必要である．「こころのリスク状態」「アットリスク精神状態」「精神病のリスクがある状態」などの言葉が用いられるかもしれない．精神病や統合失調症という言葉を用いる場合には，治療者がその言葉で何を伝えたいのか，患者や家族が理解できるわかりやすい言葉で説明する必要がある．サイコーシス，精神症などという用語を用いたり，リーフレットを補助として利用することも検討されよう．患者に，「○○という言葉を聞いたことがありますか」などと，用語についての知識やスティグマを直接確かめることが有用な場合もある．本人や家族の知識のレベルや，与えられた情報を処理するための能力に合わせた言葉の使用が必要である．

患者が示す微弱な陽性症状の説明として，「一般の人でも，6，7 人に 1 人は同様の体験をすることがある」といった，疫学的なデータに基づいた精神病様体験症状についての説明を行うなど，症状についてのノーマライゼーションを図る場合もある．リスクや予防介入の意義を説明するために

は，高血圧や糖尿病などの身体疾患での比喩を用いる方法もある．心理教育は，患者の臨床症状や治療の時期に応じて継続的に手を加えていくことが大切であり，慎重さや繊細さを心がけるべきである．

家族に対する働きかけ

家庭環境は，精神病の発症に対して促進的あるいは保護的な役割を演じることがあり，家族に対する働きかけはきわめて重要である．ARMS の若者，特に思春期の症例では家族と同居している者も多く，家族と一緒に診察を受ける機会も多い．特に治療初期には，家族からも十分に話を聞き，家族の視点を尊重しながら信頼関係を作ることが後々の治療を円滑に進めるうえでも重要となる．

統合失調症に対して行われるような，複合家族型の心理教育アプローチを ARMS の若者に適用したプログラム*3 の有効性も報告されており，このような家族への働きかけが，今後は工夫されていくべきであろう．

心理学的治療

心理学的治療は，ARMS に対する治療の基本的部分である．ARMS に対する薬物についての治験研究においても，通常は心理学的治療に付加する形で標的薬剤が投与されており，心理学的治療の影響を抜きにして薬物療法の効果を論じるのは実際的ではない．精神病の急性期においても，薬物療法に加えて心理学的治療を付加することで治療効果が上がることが知られている．

ストレス脆弱性仮説に基づいて精神病の発症をモデル化した場合，日常生活で患者が遭遇する出来事に対する心理的反応による苦痛を軽減し，ストレス因にうまく対処できるように促す介入は理にかなっている．また，ARMS においては，微弱な陽性症状に加えて，抑うつ性の気分障害，社会不安障害，強迫性障害などを I 軸診断として“合併”することが多い．むしろこのような気分障害や不安障害に付随する症状として，精神病性の症状を示す例もある．前駆期には，このような“神経症的”症状がしばしば先行するが，この時期は陽性症状と神経症的症状との相互作用の時期として記述することもできよう．神経症的症状は陽性症状の出現を促進し，正のフィードバックによって増強し合うとも考えられており，心理学的治療はこの負の連鎖を食い止める方向で作用するのかもしれない．

● 支持的精神療法

支持的精神療法は，あらゆる精神療法の基盤となる精神療法であり，患者が混乱している場合や，陰性症状が顕著な状態，あるいは構造化されたセッションに抵抗を示す場合にも適用が可能である．支持的精神療法では，精神病症状を治療の直接の標的とはせず，患者に感情的支持と社会的支援を提供することが基本となるが，患者の訴えに応じて基本的な問題解決ア

＊3
このプログラム[2]では，半日のワークショップで，前駆期についての情報，早期介入の根拠，精神障害の生物学的基盤，ストレス脆弱性仮説，神経薬理学的治療，心理学的治療，学校介入，保護的環境づくりの推奨などが心理教育される．その後，2 週ごとに 90 分のグループセッションが 9 か月間施行され，ソーシャル・スキル，コミュニケーション・スキル，問題解決技能の向上を図り，家族が症状にうまく対処できるように支援する．

Key words
前駆期での家族の感情表出（expressed emotion：EE）
家族の EE は，前駆期から顕在発症後の数年間でダイナミックに変化する[7]．若者の能力の低下は，親の保護的な態度を自然と増大させるが，慢性期とは異なりこの時期の家族の感情的巻き込まれは，肯定的な発言や暖かさと同様に症状の軽減や社会的機能の改善に寄与しうる[8]．しかし，前駆期の長期化や，陰性症状や機能障害の増大に従い，一部の家族ではフラストレーションが生じてしまう．家族の EE の増大は，患者に否定的な感情や行動を引き起こし，家族間での正のフィードバックの過程が負の連鎖をいっそう拡大し，病初期の数年間で批判や敵意の度合いが上昇する．したがって，家族の批判や敵意が固定化する前に，家族が適切に患者に対処できるように手助けする介入が必要となる．

プローチも実施される．支持的精神療法によって，ARMS の精神症状や社会機能の種々の評価項目が改善することが知られている．

●認知行動療法

認知行動理論に基づく治療法は，総称して認知行動療法（CBT）と呼ばれるが，治療の実際は，適用される対象や治療を行う条件などに応じてさまざまである．

ARMS に対する CBT の有効性を示したマンチェスターの EDIE における CBT[*4] は，Beck の認知療法に基づいており，患者が症状の引き金となる可能性のある因子をどのように見つけるのか理解し，その出来事に対するものの見方が感情的・行動的反応を決定することを理解するように働きかけ，ケース・フォーミュレーションに基づいた問題指向的アプローチを重視している．

EDIE による無作為化対照試験では，1 年間の精神病移行率は，観察群の 26 %と比べて，6 か月間 CBT を受けた群が 6 %で有意に少なく，CBT が精神病への移行を短期間予防あるいは遅延させる効果をもつことが示された[4]．一方，3 年後の追跡調査では，抗精神病薬の処方例は CBT 群で有意に少なかったが，精神病移行率については両群間に差を認めなかった[9]．この結果からは，6 か月間の CBT による介入効果は 3 年後にも認められたが，予防効果については 3 年後には消失していることがわかる[1]．

一方，メルボルンの PACE クリニックで実施されているものは，ストレス・マネジメント，陽性症状，陰性症状/抑うつ，その他の併存症の 4 つのモジュールから成っており，ストレス・マネジメントが中心にすえられている．PACE では，少量のリスペリドン投与と CBT を組み合わせた治療法によって，精神病の発症が抑制されることが示されている．

また，ドイツ・ケルン大学のグループは，独自の基準による基底症状や素因群によって構成される早期初回前駆状態（early initial prodromal state）に対して，①心理教育やストレス・マネジメントを含む個人療法，②集団療法，③注意・集中・記憶などの訓練を行う認知リメディエーション（cognitive remediation），④家族への心理教育，の 4 つのモジュールから成る包括的な CBT を実施している．

●心理学的治療の構成要素

欧米で実施されている心理学的治療の多くは，CBT のように構造化されたセッションを専門の心理士が短期間実施する形式のものが多い．しかし，CBT などを専門に行う心理士はわが国の臨床現場では一般的ではなく，構造化されたセッションのために継続的に十分な時間をとることは困難であろう．治療環境が許されるのであれば，そのような独立したセッションによって治療効果を向上させることが望ましいが，実際には，主治医である精神科医によって，利用できる治療技法を限られた時間のなかで組み合わせ，個々の患者に合わせた介入が実施されることが一般的であろう．

＊4
CBT では，45 ～ 60 分のセッションが 20 ～ 30 回実施されるのが一般的である．EDIE では，6 か月間の CBT による介入の最大セッション数は 26 回で，実際の平均は約 12 回であった．

Key words
Beck の認知療法
Beck の認知療法モデルは以下の要素によって構成される[3]．
①障害の発症と持続を説明する認知モデルに基づく．
②ケース・フォーミュレーションに基づく．
③セッションは構造化されている．
④問題と目標を共有し，これに基づく．
⑤クライアントが治療過程を理解できるような教育的要素を含む．
⑥ソクラテス的対話法を用い，治療者に導かれながら患者が発見に至るプロセスを重視する．
⑦ホームワークを課す．
⑧治療時間や治療期間を設定する．

以下に，ARMS に対する心理学的治療の構成要素や技法的側面を，CBT で用いられるアプローチ[3,6]を中心に取り上げて述べることとする．

治療関係の構築

精神科治療において初期の治療関係づくりが重要であることには論を待たない．英語圏では engagement という言葉を用いてこの治療プロセスに特別な関心が払われており，ARMS の心理治療においてもその重要性が強調されている．McGlashan ら[2]は，「治療関係づくりは，治療者と患者とのあいだに信頼関係に基づいた人間関係を構築し，彼らが必要な診療の予約に継続的に来ることに，十分な安心感とメリットを見出すことができるように手助けすることが，最大の目的である」と述べている．患者に必要な介入を施そうとするのであれば，継続的なかかわりをもつための関係づくりに，まずは最大の関心が払われるべきである．

治療関係づくりのためには，患者にとって優先度の高い問題に取り組む問題指向的アプローチが有効である．住居や経済的問題，家庭内不和，対人トラブル，学業や仕事上の問題など，現実的・日常的な問題の危機介入やケース・マネジメントを通して患者を援助する支持的な介入が患者との信頼関係を発展させる．

ARMS においては，精神病症状が一過性であったり，臨床閾値下であっても，コミュニケーションや情報処理に多大な影響を与えることがあり，その基盤には認知機能の障害が関与する場合もある．患者が治療者の話を理解しているのか，そして治療者が患者の話を理解しているのか確認するために，聞き返しを行ったり，要約を行うなど定期的なフィードバックが勧められている．このような共同作業的姿勢は，患者が自分の立場が認められている，話を聞いてもらっている，理解されている，治療者が自分の言うことに本当に関心をもっているという感覚を強めるために役立つ．

治療を行う場所や時間設定が，治療関係の構築に影響することを認識しておくことは重要である．この群に対する治療では，予約のキャンセルや時間変更がよく起こるが，治療者は，こうしたことに寛容で，一般的な環境で容認される範囲を超えて予約を提案し続けることが必要とされている[3]．

問題指向的アプローチ

患者が優先すべきとみなしている問題に焦点をあて，共同で取り組むことは重要である．精神病的症状のような異常な体験のために ARMS とみなされる場合であっても，患者はそのことを優先的な問題とは考えていないことがしばしばである．問題指向的アプローチは，治療関係を構築し維持するうえでもきわめて重要であり，患者と問題を共有し，これに応じて必要な介入を行っていく．

ケース・フォーミュレーション（症例の概念化/定式化）

ケース・フォーミュレーションでは，問題となっている症状や状況など

Key words

問題・目標リストの活用

治療セッションにおいて網羅的な問題リストの一覧を作成し，優先順位をつけ，これを目標に置き換える作業には，時間をかけるだけの十分な価値がある．目標は具体的（specific），測定可能（measurable），達成可能（achievable），現実的（realistic），時間の設定がある（time limited）形にまとめる（SMART）[3]ことが望ましい．目標に取り組む際には，短期間のうちに達成できそうな問題から取り組むことがコツである．早い段階で成功体験を共有することができれば，患者は治療に前向きに取り組むようになり，将来の目標に対しても希望をもてるようになる．

を取り出し，治療者と患者が共同作業を行いながら，その問題がなぜ起こり，なぜ持続するのか仮説を立てる．認知療法*5では，認知モデルに基づいて，問題の認知・感情・行動・身体の各因子を取り出し，それぞれがどのように作用し合っているのか図式的に把握する作業が行われる．これは，包括的である場合もあれば，知覚異常，被害念慮，社会不安，抑うつなどの特定の精神症状について検討される場合もある．この作業を通して，治療者と患者との共同作業が促進され，お互いに問題点を共有し確認することができ，フォーミュレーションに基づいた治療計画が可能となる．認知療法では，フォーミュレーションに基づいた介入を行うことを原則としており[3]，治療が進むにつれ，新たな情報に基づいてフォーミュレーションは修正されていく．

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認知療法は，認知行動療法に含められるが，狭義には，Beck の認知療法などのように，治療において認知的側面を重視する立場の治療法を総称しており，治療法には一定の枠組みがある．

ストレス・マネジメント

ストレスと対処についての教育，リラクゼーション訓練などに加え，CBT の要素を取り入れた「ストレスレベルの把握とモニタリング」「ストレスに対する不適切な対処法の把握と適切な対処法への修正」「自覚的なストレスや強い不安と関連する非機能的な思考（dysfunctional thought）の同定と認知再構成法」などが症例に応じて用いられる．

ノーマライゼーション

ノーマライゼーションの技法は，精神病症状が正常過程との連続体上に位置するという考えに依拠しており，統合失調症の認知療法において導入されている．ARMS においても，ノーマライゼーションに必要な情報を提供することで，微弱な陽性症状に対する破局的なとらえ方（たとえば，「狂ってしまうのではないかという恐怖」）をしないように働きかけ，体験に対するスティグマや苦痛を減らすことが役立つ．たとえば，一般の人々でも，精神病様の体験を経験する人の割合が比較的高いことや，心的外傷体験やストレスの強い出来事の後に「声」を聞く体験をする人が多いことなどの情報を伝えることが役立つ場合がある．

ノーマライゼーションの技法は，単に情報伝達の側面にとどまるのではなく，治療者の姿勢や態度にもかかわる．患者の体験を詳細に聞くことで，体験と状況との関連を結びつけて理解することが大切である．ノーマライゼーションの技法は，単に「大丈夫」「どうにかなるよ」などと根拠に乏しい安心感を与えることや，患者の問題を軽視することとは異なる点に注意すべきであり，患者の苦痛は真摯に受け止められなければならない[6]．

代わりの説明を見つける

前駆期では，異常な体験について十分に吟味された説明を患者が持ち合わせていないことが多い．彼らが体験する微弱な陽性症状の説明として可能性のある選択肢をあげるように促し，それぞれの説明を支持する証拠とそれに反する証拠を評価する介入が有効なことがある．この介入の目的は，より苦痛が小さくより正確な説明を見つける技術を本人が獲得するように

手助けすることである．ここで大切なことは，ソクラテス的対話法を用いて，患者が自らさまざまな選択肢を考え，自らの結論に至るように質問を投げかけることである．それぞれの選択肢について確信の度合いを0～100％の尺度で数値化させることで，自らのものの見方を相対化することができ，変化の度合いを評価することが可能になる．

安全行動への行動的介入

不安障害の患者では，恐れている状況を回避するために特定の安全行動を日常的に用いていることがしばしばあるが，ARMSにおいても微弱な陽性症状と関連した苦痛が安全行動によって維持される場合がある．安全行動について詳しい聞き取りを行い，これが同定されたら，その短期的，長期的な有用性を検討するために行動実験の計画と実施を試みることが役立つことがある．これは，患者に苦痛を引き起こす非機能的な解釈の誤りを正す効果がある．ただし，患者にとって保護的に働いている症状を無理に取り除くことは，病状の悪化を招く危険性もあり，注意が必要である．

中核信念

認知療法では，その人の基底的な層にある信念を中核信念と呼ぶが，ARMSの患者では「自分は人と違っている」「自分はおかしい，変わっている」という中核信念が見出されることが多い．この信念そのものの修正が必ずしも必要となるわけではないが，患者がそのような信念をもつに至った個人的な体験やその意味を治療中に同定し理解していく過程は重要とされている．「もし，人と違っているとしたら，それはあなたにとってどのような意味をもつのでしょうか」などの質問を重ねていく下向き矢印法などの技法が，中核信念の同定のために用いられる．

併存する症状を標的にした介入

ARMSでは，微弱な陽性症状よりも，むしろ気分，不安症状が主症状として訴えられる場合もしばしばである．強迫性障害に対して暴露反応妨害法を用いたり，社会不安障害に対してDavidとClarkのモデルに従ったCBTを適用するなど，個々の症状に対して，最も適切な認知行動モデルを用いて，臨機応変に対処することが役立つ場合がある．

おわりに

統合失調症の前駆期を前方視的に正確に把握することが困難な現状においては，ARMSを標的にした治療介入は，兆候型の予防介入として現時点では最も受け入れられているアプローチである．しかし，ARMSにおいても，短期間で精神病に移行する者は半数にも満たない点には留意すべきである．また，ARMSの基準を満たさないが，実際には前駆期にある患者にわれわれが遭遇する場合もある．前駆期を疑う患者やARMSの患者に取り組む場合には，確定診断のついた統合失調症とは異なる対応が必要であ

り，症状や経過の多様性をふまえたうえで，楽観的で，回復に焦点をあてた臨機応変な治療アプローチが必要である．

（松本和紀）

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