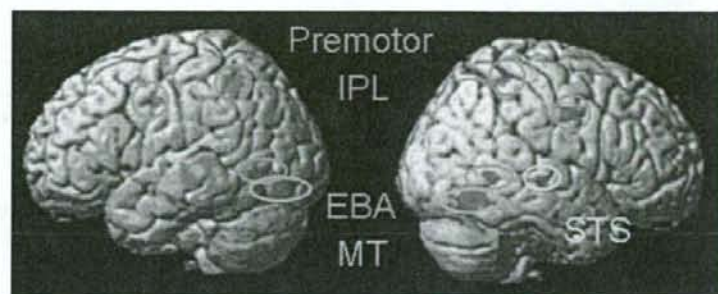


Figure 2. Brain activations in response to sports-related motion minus sports-unrelated motion. Significant activations in extrastriate body area (EBA), middle temporal (MT), superior temporal sulcus (STS), inferior parietal lobule (IPL) and premotor areas are shown. Within the images, L indicates left and R indicates right.



$P < 0.001$, uncorrected, and an extent threshold of 10 contiguous voxels.

DISCUSSION

This study demonstrated that BR motion produced greater activation in the posterior temporal–occipital cortex (MT and EBA), STS and IPL than BU motion. BR motion was complex goal-directed biological motion with understandable intention, whereas BU motion was complex non-goal-directed biological motion. Therefore, the greater activation of STS is fairly predicted because it is widely accepted that STS is involved in detection of goal-directed actions and intention of others,^{3,8,9} and even a walking robot could activate STS.¹⁹ The greater activation of IPL, as a part of human MNS, was also predicted. Human neuroimaging and monkey studies have supported the view that when we observe others' actions, the action is internally represented through our own motor system including MNS.^{5,18,20} It has been suggested that MNS may participate in understanding and imitation of action through a mechanism by which observed actions are automatically matched with internal motor representation (action repertoire),^{5,6,21–23} and IPL neurons respond differently to similar actions with various intentions.²⁴

The novel finding in the present study is that EBA and MT responded more strongly to BR motion than BU motion, although both BR motion and BU motion were complex biological motions containing an identical number of bodies or body parts. Neuroimaging studies about biological motion have demonstrated that STS plays a crucial role in processing biological motion and is important for detecting intention of others. But the studies have consistently reported the involvement of other brain regions such as EBA and MT,^{25,26} and the exact role of these regions in processing biological motion has been unclear.

Originally, EBA was identified as an area that responds selectively to human bodies and body parts. In that study, at the same time, EBA responded more strongly to natural motion than to artificial motion.¹⁰ Thereafter, the role of EBA in processing human actions has been the focus of many discussions. The static representation hypothesis is that EBA responds simply to static snapshots of the individual posture that comprise whole-body actions.²⁷ In contrast, the dynamic representation hypothesis is that EBA is directly involved in representing the dynamic aspects of human motions as part of a system for inferring the action and intention of others.^{17,18} Astafiev *et al.* demonstrated that EBA also responded to self-produced body movements, even if the body part is not visible.¹⁶ Jackson *et al.* reported that, compared to observation of actions, EBA activation was enhanced during imitation.¹⁷ Furthermore, the motivation to act has been shown to modulate EBA activity.²⁸ These studies proposed an extended role for EBA, involving the planning, execution and imagination of actions. In favor of the latter hypothesis, the present result suggests that EBA might contribute to the understanding of goal-directed actions, being located at the entry of human MNS.

MT has been known to respond selectively to moving stimuli,¹¹ and an fMRI study reported that MT responded equally to meaningful and non-meaningful actions,¹⁹ suggesting that MT processes low-level physical properties or information of moving stimuli. But it was reported that MT responded to static images of implied motion²⁹ and that the MT responses to static body images were greater than to other object images.^{30,31} From these findings it is suggested that face and body figural information might project to MT.^{26,32} The present findings of enhanced activations in MT along with EBA may support this view, although several studies have reported substantial overlapping between EBA and MT.^{14,30,31}

In conclusion, EBA might be located at the entry of human MNS through which dynamic aspects of human motions are represented and contribute to the understanding of others' actions. The present results merit further investigation of the function of EBA in neuropsychiatric disorders such as schizophrenia and autism.

ACKNOWLEDGMENTS

This study was supported by a consignment expense for Molecular Imaging Program on Research Base for PET Diagnosis from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government, a Grant-in-Aid for Scientific Research from MEXT (15390438), a research grant for nervous and mental disorders (14B-3), and a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H19-KOKORO-004) from the Japanese Ministry of Health, Labor and Welfare.

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

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ARTICLE INFO

Article history:

Received 3 July 2008

Received in revised form 14 October 2008

Accepted 8 November 2008

Available online 4 December 2008

Keywords:

Schizophrenia

Dopamine synthesis

[¹¹C]DOPA

Positron emission tomography (PET)

PANSS

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-¹¹C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as *k*₁ 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*₁ values in patients than in controls in the left caudate nucleus, but not in the other regions. The *k*₁ 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*₁ 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.

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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) D₂ receptor (D₂R) binding by the use of PET. Although studies investigating D₂R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D₂R 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-[¹⁸F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashaf et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[¹¹C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[¹⁸F]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 (Elkashaf 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-[¹¹C]DOPA does not take place readily and rapidly when compared with 6-[¹⁸F]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-[¹¹C]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-[¹¹C]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 out-patient 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-[¹¹C]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 ⁶⁸Ge–⁶⁸Ga 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-[¹¹C]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 \pm 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:

$$\frac{C_i(t)}{C_i^*(t)} = k_i \frac{\int_0^t C_i^*(\tau) d\tau}{C_i^*(t)} + F_{i,t^*}$$

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

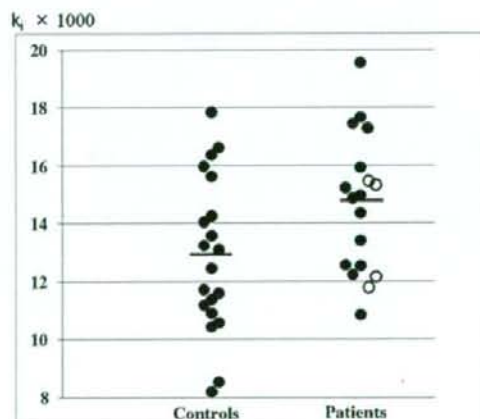


Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those 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	
		<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
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- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$. The duration of illness and the PANSS scores are also shown in Table 1.

3.2. Regional L- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$ 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- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$ 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- $[\text{F}^{18}]\text{fluoro-L-DOPA}$ 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- $[\text{F}^{18}]\text{fluoro-L-DOPA}$ and L- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$ 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- $[\text{F}^{18}]\text{fluoro-L-DOPA}$ 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- $[\beta\text{-}^{11}\text{C}]\text{DOPA}$ 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 (Andreassen 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 D₂ 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-[¹⁸F]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 D₂R 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-[¹⁸F]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 -¹¹C]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.

Role of funding source

This study was supported by a consignment expense for the Molecular Imaging Program on “Research Base for Exploring New Drugs” from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government.

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.

Acknowledgement

We thank Mr. Katsuyuki Tanimoto, Mr. Takahiro Shiraishi, and Ms. Yoshiko Fukushima for their assistance in performing the PET experiments at the National Institute of Radiological Sciences.

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Research

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Pathway to psychiatric care in Japan: a multicenter observational study

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Published: 26 September 2008

Received: 23 August 2008

International Journal of Mental Health Systems 2008, 2:14 doi:10.1186/1752-4458-2-14

Accepted: 26 September 2008

This article is available from: <http://www.ijmhs.com/content/2/1/14>

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Abstract

Background: This study examines pathways to psychiatric care in Japan using the same method as the collaborative study carried out in 1991 under the auspices of the World Health Organization.

Methods: Thirteen psychiatric facilities in Japan were involved. Of the 228 patients who contacted psychiatric facilities with any psychiatric illness, eighty four visiting psychiatric facilities for the first time were enrolled. Pathways to psychiatric care, delays from the onset of illness to treatment prior to reaching psychiatrists were surveyed.

Results: Thirty three patients (39.4%) directly accessed mental health professionals, 32 patients (38.1%) reached them via general hospital, and 13 patients (15.5%) via private practitioners. The patients who consulted mental health professionals as their first carers took a longer time before consulting psychiatrists than the patients who consulted non-mental health professionals as their first carers. The patients who presented somatic symptoms as their main problem experienced longer delay from the onset of illness to psychiatric care than the patients who complained about depressive or anxiety symptoms. Prior to the visit to mental health professionals, patients were rarely informed about their diagnosis and did not receive appropriate treatments from their physicians. Private practitioners were more likely to prescribe psychotropics than physicians in general hospitals, but were less likely to inform their patients of their diagnosis.

Conclusion: This first pathway to psychiatric care study in Japan demonstrated that referral pathway in Japan heavily relies on medical resources. The study indicates possible fields and gives indications, underlining the importance of improving skills and knowledge that will facilitate the recognition of psychiatric disorders presenting with somatic and depressive symptoms in the general health care system and by private practitioners.

Background

An understanding of the way in which people seek care for mental disorders is important for planning mental health services, for the organization of training and for the organization of referrals to psychiatrists from other sources of health and social care. Goldberg and Huxley [1] proposed the 5 level model, which assumes that people with psychiatric problems start seeking care by consulting their general practitioner, who may refer them to psychiatric facilities. However, descriptive studies regarding this issue [2,3] demonstrated that people with psychiatric problems follow a variety of pathways before they reach mental health professionals, and that their pathways are influenced by various factors including conventions governing referral, relationships between mental health professionals and other sources of help, and the availability of and accessibility to mental health facilities and other helping agencies. Delays before people with mental illness receive appropriate care are also affected by several demographic factors, by diagnosis of the patients and by pathways they follow to reach psychiatrists.

The pathway study is a quick, useful and inexpensive method of studying help-seeking behavior of people with a mental illness. Pathway studies have been conducted in many countries but, to our knowledge, no study of pathways or people with mental health problems had been done in Japan. Yet, pathway studies in Japan are of particular interest because of the special features of the health system of Japan in which there are no general practitioners, and where patients are allowed to see any doctor of their choice.

Methods

Procedure

We have used the method developed for the World Health Organization multicenter pathway study [1], albeit with a

shorter study period. All consecutive patients who visited mental health services for the first time within one calendar week between October 2003 and January 2004 were enrolled. A semi-structured interview based on an encounter form developed in the WHO collaborative study was conducted by mental health professionals with all the patients enrolled. We translated the encounter form and revised it slightly to adjust it to the situation in Japan. The encounter form served to record demographic data, the main problems presented by the patients, the source and type of care they received before they saw the mental health professional, and the length of time between the occurrence of their mental health problems and their contact with professional carers. The length of time at each step of care was also recorded. Psychiatric diagnoses according to ICD-10, and the total duration of illness were filled in by the psychiatrist in charge.

The areas and participating centers

The participating centers were thirteen hospitals, of which seven were university hospitals, one a public general hospital and five mental hospitals. The study centers were in 12 cities across the nation. Each of them was the main provider of psychiatric services in each area (although psychiatric facilities may have also been located in their areas). The cities and their population, the number of psychiatric beds per 100,000 population and psychiatrists per 10,000 population are shown in Table 1.

The study was conducted under the auspices of the Japan Young Psychiatrist Organization (JYPO). The JYPO is a nationwide group of young psychiatrists aiming to promote academic development and networking in the field of psychiatry.

This study was approved by the institutional review boards of each participating center, and all subjects gave

Table 1: Participating centers

Name of institution	Type of institution	City	Population (thousand)	Psychiatric beds per 10,000 population	Psychiatric doctors per 100,000 population
Sapporo Medical University Hospital	UH	Sapporo	1,817	46	16
Iwate Medical University Hospital	UH	Morioka	288	50	15
Yokohama City University Medical Center	UH	Yokohama	3,381	16	8
Kansai Medical University Hospital	UH	Moriguchi	150	15	8
Nagasaki University Hospital	UH	Nagasaki	421	69	18
Kurume University Hospital	UH	Kurume	235	63	37
Fukuoka University Hospital	UH	Fukuoka	1,330	35	18
Wakkanai Municipal Hospital	GH	Wakkanai	44	23	9
Asai Hospital	MH	Togane	59	23	24
Sakuragaoka Memorial Hospital	MH	Tama	145	75	26
Zikei Hospital	MH	Okayama	621	49	24
Kochi Prefectural Geiyo Hospital	MH	Aki	21	72	28
Okawa Hospital	MH	Buzen	29	147	17
Whole nation			125,613	28.2	10.2

UH: University Hospital, GH: General Hospital, MH: Mental Hospital

their written informed consent after having been given a full description of the study.

Data analysis

The routes taken by individual patients were brought together to produce a "Pathway Diagram". The number of patients taking each step on the pathways was mapped onto the diagram along with the delays occurring at each step. Delays were compared among major pathways, among different diagnostic groups and among presenting problems. We used median values when comparing delays because the distribution of delay was heavily skewed. Fisher's exact test was used for categorical data and Mann-Whitney non-parametric test was used for continuous data, using the SPSS version 15.0J software (SPSS Inc., Chicago, USA).

Results

Subject data

Two hundred and twenty eight patients visited the participating centers for the first time during the study period. Written informed consent was obtained from 144 patients (68%), of which 84 patients (male 34: female 50) contacted psychiatric services for the first time because of the presenting problem (Figure 1). Sixty seven were seen at university hospitals, 3 at the public general hospital and 14 at mental hospitals. There were no significant differ-

ences in age and gender between subjects who consented and not consented to participate in the study.

Main problem presented and diagnosis given by mental health professionals

The main problems presented to the first carer are listed in Table 2. The most frequent presenting problems were somatic symptoms and depression (19 patients: 22.8% each), followed by social problems (13 patients: 15.6%) and anxiety (12 patients: 14.5%). Distribution of diagnoses on ICD-10 is shown in Table 3. The most frequent diagnoses using ICD-10 criteria given by mental health professionals were mood disorders (F3) (21 patients: 25.0%), neurotic, stress-related and somatoform disorders (F4) (20 patients: 23.8%) and organic, including symptomatic, mental disorders (F0) (12 patients: 14.5%). Of 12 patients with F0 diagnosis, 7 patients were diagnosed as having dementia.

Pathway diagram

The sources of care utilized by the patients before they presented to psychiatric services are shown in Figure 2. Three major pathways were used - the direct pathway (contacting the mental health professional as first carer), the pathway via general hospitals ("GH pathway"), and the pathway via private practitioners ("PP pathway") comprise approximately 90% of the total subjects. Thirty three

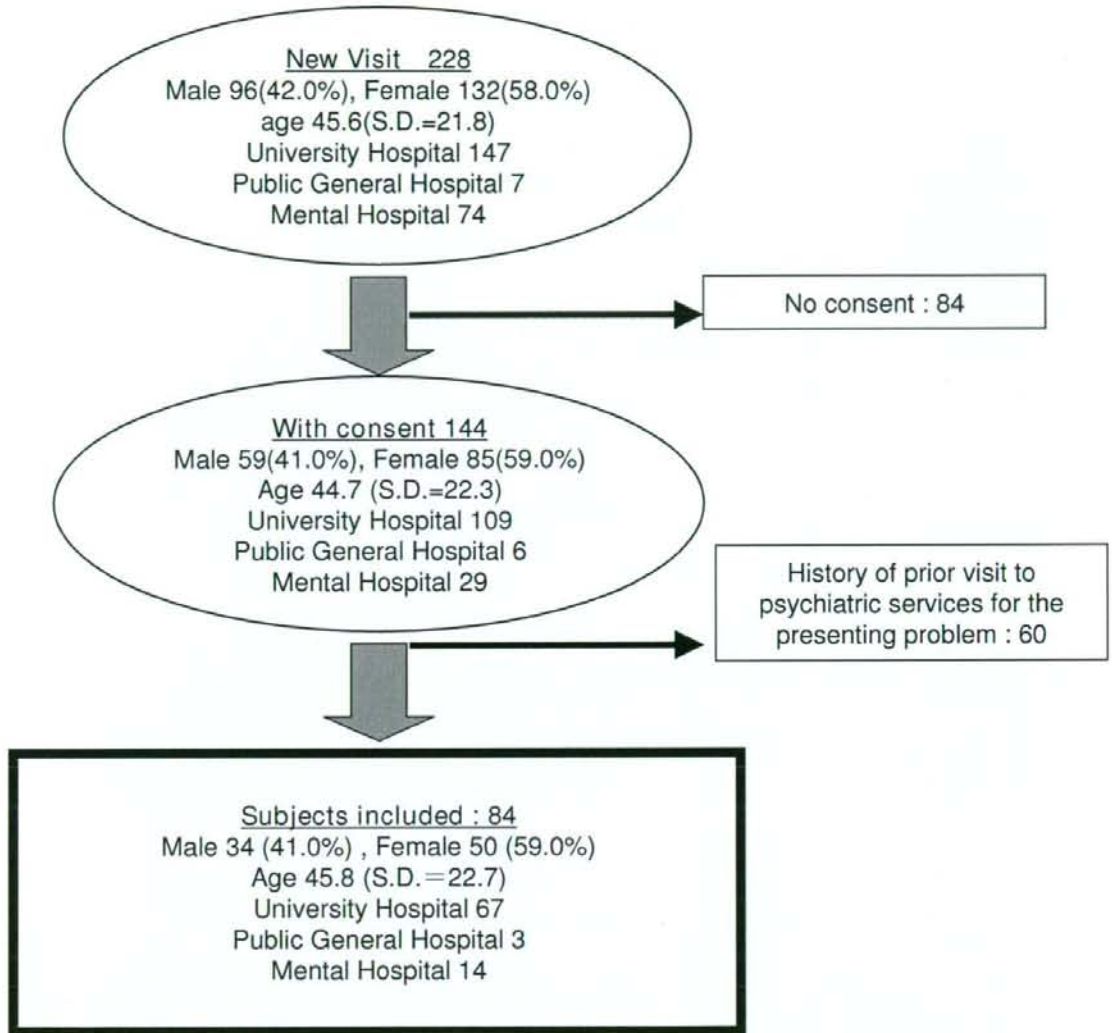


Figure 1
Inclusion procedure and demographics of the subjects. Figure legend text.

patients (39.4%) directly accessed mental health professionals, 32 patients (38.1%) reached them via GH pathway, and 13 patients (15.5%) via PP pathway. A small number of patients were referred from educational facilities (school teachers, university health center), a life support center and a public health nurse in the community.

Delays to psychiatric care

The mean number of carers consulted prior to mental health professionals was 0.8 (S.D. = 0.9). The patients

who first consulted general hospital saw average of 1.1 carers (S.D. = 0.4), and those who consulted private practitioners saw average of 1.5 carers (S.D. = 1.0) before they saw mental health professionals.

The distribution of delay has a long tail with progressively smaller numbers of patients having longer delays, inflating the mean delay to 87.4 weeks (S.D. = 284.8). Therefore, we adopted the same methodology as previous reports, and used median values. The median delays

Table 2: Type of first carer and main problems presented

	Somatic	Depression	Social	Anxiety	Altered consciousness	Psychotic	Dementia related	Others	Total (%)
Mental Health Professionals	5	10	6	9	0	0	1	2	33 (39.3)
Other Carers	14	9	7	3	5	4	3	6	51 (60.7)
Total (%)	19 (22.8)	19 (22.8)	13 (15.6)	12 (14.5)	5 (6.0)	4 (4.8)	4 (4.8)	8 (9.5)	84 (100)

among total subjects and delays in main pathways are shown in Table 4. The median delay between the onset of the problem and contact with the first carer was two weeks; between the first carer and mental health professionals, zero week; and between the onset of the problem and consultation with mental health professionals were eight weeks.

The median delay between the onset and consultation to the first carer was longest in direct pathway (8 weeks), and was significantly longer than other pathways (1 week in GH Pathway and 4 weeks in PP Pathway). The median delays between the first carer (general hospital doctor or Private Practitioner) and mental health professionals were 0 week. The median delays were not significantly different among three major pathways.

Factors affecting the choice of pathway and delays

Table 5 shows relationship between presenting symptoms, choice of first carer and delays to psychiatric care. Patients with anxiety are more likely to go directly to mental health professionals, whereas patients with somatic symptoms were likely to firstly consult carers other than mental health professionals. Patients with depressive symptoms lie in between ($p < 0.05$).

The patients with somatic symptoms take longer time and see larger number of carers before they reach mental health professionals, compared with those with anxiety symptoms. Age, gender, financial level, whether single or

cohabitant, or past history of psychiatric disorder do not affect delays.

Treatment by prior carers

Of 58 patients who were seen by non-psychiatric physicians, 37 patients were seen by general hospital doctors and 21 patients by private practitioners. We compared referral rate to mental health professionals, information about diagnosis given to patients, psychoeducation and medications given by hospital doctors and private practitioners.

(a) Referral to mental health professionals

Thirty two out of 37 patients who consulted general hospitals and 13 out of 21 patients who consulted private practitioners visited mental health professionals as their next carer. These patients are categorized into two groups: those who visited mental health professionals on their own decision (self-referral) and those who were referred by physicians (physician-referral). Twenty six out of 32 patients (81.3%) were referred by physician in general hospitals and 6 out of 13 (46.2%) by private practitioners ($p < 0.05$).

(b) Informed diagnoses and psychoeducation

Thirty one out of 58 patients were informed about their diagnosis (19 out of 28 at GH, 12 out of 21 at PP). Because of the small sample size, we limited statistical analysis to mood disorders and neurotic disorders. Accurate diagnoses were more likely to be told to patients by general

Table 3: Type of first carer and diagnosis given by mental health professionals

	F0	F2	F3	F4	F5	F6	Others	Total (%)
Direct Access to MHP	4	2	9	10	2	1	5	33 (39.4)
Indirect Access to MHP	8	2	12	10	3	2	14	51 (60.8)
Total (%)	12 (14.5)	4 (4.8)	21 (25.0)	20 (23.8)	5 (6.0)	3 (3.6)	19 (22.8)	84 (100)

Diagnosis based on ICD-10

F0: Organic, including symptomatic, mental disorders

F2: Schizophrenia, schizotypal and delusional disorders

F3: Mood disorders

F4: Neurotic, stress-related and somatoform disorders

F5: Behavioural syndromes associated with physiological disturbances and physical factors

F6: Disorders of adult personality and behaviour

MHP: Mental Health Professionals

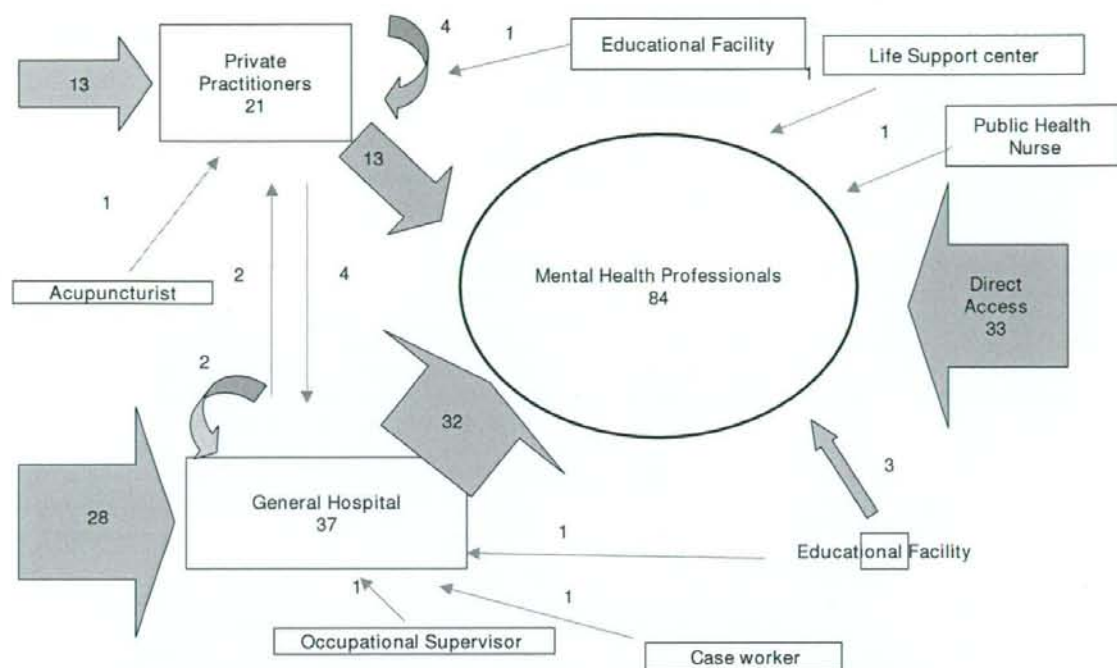


Figure 2
The Pathway Diagram. Figures indicate numbers of subjects who took each pathway or consulted each carer. Curved arrows indicate recursive pathways, where patients have gone from one to another of the same type of carer.

hospital doctors than by private practitioners. Only 3 out of 11 patients with depression seen by general hospital doctors were told their diagnosis and none was informed about diagnosis by private practitioners. In patients with anxiety, none out of 9 in general hospitals and only 1 out of 5 seen by private practitioners were told that they had neurotic disorders (Table 6).

(c) Medications
 Eleven out of 58 patients (19.0%) received psychotropic medications; 6 out of 37 (16.2%) by general hospital doctors, (hypnotics 2, antidepressants 4), and 5 out of 21 (23.8%) by private practitioners (anxiolytics only).

Table 4: First carer, delays to psychiatric care and number of carers before patients reach mental health professionals

First carer	Number of patients	Delays (median weeks)			Mean Number of carers prior to Mental Health Professionals (S.D.)
		Onset to first carer	First carer to Mental Health Professionals	Onset to Mental Health Professionals	
Mental Health Professionals	33	8 ^{a*} , ^{b*}	-	8	-
General Hospital Doctors	28	1 ^{a*}	1	3	1.1 (0.4)
Private Practitioners	13	4 ^{b*}	1	8.5	1.5 (1.0)
Total	84	2	0	8	0.8 (0.9)

a*, b*: p < 0.1 : median test

Table 5: Main presented problems, first carer, delay and number of carers before patients reach mental health professionals

	First carer				Median delay (weeks)			Mean Number of Carers prior to Mental Health Professionals (S.D.)
	Mental Health Professionals	General Hospital Doctors	Private Practitioners	others	Onset to First Carer	First Carer to Mental Health Professionals	Onset to Mental Health Professionals	
Somatic (n = 19)	5 ^{a*}	8	3	3	3.0	1.0 ^{b*}	9.0	1.2 ^{c*} (1.0)
Depressive (n = 19)	10 ^{a*}	7	1	1	4.0	0	8.0	0.3 (0.5)
Anxiety (n = 12)	9 ^{a*}	3	0	0	2.5	0 ^{b*}	20.0	0.6 ^{c*} (0.8)
Total (n = 84)	33	27	13	11	2.0	0	8.0	0.8 (0.9)

a*: p < 0.05; Fisher's exact test, b*: p < 0.05; Median test, c*: p < 0.05; Mann-Whitney's U test

Discussion

To our knowledge, this is the first multicenter study of pathways to psychiatric care in Japan. Our study provides a rough sketch of referral pathways to psychiatric care and some information about delays (and factors that influence them), treatments and psychoeducation given to the patients. Japan is unique in that it lacks general practitioners. We lack in training in general practice and most physicians in Japan are specialists in some field. Japan is also unique in that it employs free-referral medical system. That means, patients are allowed to see any hospital, any doctor of any subspecialty. Note that these two characteristics are quite important to understand the feature.

This diagnostic distribution is similar to those of previous pathway studies conducted in west European countries, including Spain[2], Italy[3] and United Kingdom[4].

The common presenting problems were somatic symptoms, depressive symptoms and anxiety symptoms. This is also similar to findings or previous pathways studies in developing and developed countries.

The pathway diagram demonstrates that, in Japan, 40% of all subjects have directly access to mental health professionals. Pathway studies have demonstrated that pathway to psychiatric care follow three patterns. The first pattern is dominated by the role of primary care physicians. Most patients first contact their general practitioner who refers

Table 6: Referral rate and treatments by prior carers

	Number of patients	Patients who visited MHPs as the next step	Patients referred to MHPs by prior carers	Psychiatric diagnosis		Treatment		
				Informed to patients	Accurate diagnosis given	Benzodiazepines	Anti-depressants	Anti-psychotics
General Hospital Doctors				19	F3 3/11 F4 0/9	2	4	0
Private Practitioners	21	13*	6*	12	F3 0/4 F4 1/5	5	0	0
Total	58	45	32	31	F3 3/15 F4 1/14	7	4	0

F3: Mood disorders, F4: Neurotic, stress-related and somatoform disorders

MHPs: Mental Health Professionals

* P < 0.05 : Fisher's exact test

them to mental health professionals. This pattern is seen in west and east European countries (Cantabria and Granada in Spain[2], Manchester in England[4], Benesov-Kromeriz in Czechoslovakia[5], Sofia in Bulgaria[5], Turgu Mures in Romania[5]), Aden in Yemen[2], Mexico City in Mexico[2], Havana in Cuba[2] and Sydney in Australia[6]. The second pattern is seen in Bali[7] and Ujung-Pandang (Indonesia)[2], Bangalore (India)[2], Harare (Zimbabwe)[2], Kwara (Nigeria)[8] and Rawalpindi (Pakistan)[2], where native healers play an important role in referral pathway. The third pattern is seen in Ankara (Turkey)[9], Lower-Silesia (Poland)[10], Verona (Italy)[3], where patients are allowed to see any carer of their choice and are likely to have directly access to mental health professionals. The nations of this pattern are likely to have larger proportion of patients who directly access mental health professionals. Our results are similar to those in countries with the third pattern. In Japan, patients are allowed to access any medical facilities of their choice, and patients with psychiatric problems prefer to see physicians in general hospitals rather than private practitioners. In contrast, in countries in which people are supposed to see general practitioners before they are seen by specialists (such as Spain[2], United Kingdom[4], Portugal[10], Czechoslovakia[2], and Australia[6]), the pathway to mental health professionals via private practitioners is the most frequent and direct access is an exception.

Direct access to mental health professionals has both advantages and disadvantages. In the Goldberg and Huxley model[1], general practitioners are expected to function as "gate keepers" to apportion patients with a more severe form of illness to higher levels of specialization by keeping milder patients at lower levels. This gate-keeping role is supposed to enable psychiatrists to concentrate on patients with more severe forms of illness. Direct accessibility to mental health professionals may lead to wasteful use of the time of highly specialized professionals who would treat milder forms of illness which could be very well done by general practitioners. Such an arrangement would thus increase the cost of care and deteriorate medical economical efficiency. On the other hands, direct accessibility to mental health professionals may shorten the total delay between the onset of symptom and arrival at mental health professionals for patients who may have milder symptoms in the beginning of their illness but who do not recover as well when treated by general practitioners.

There are two types of delay in reaching psychiatric care. The first type of delay is the delay between the onset of the problem and the contact with the first carer. The length of this type of delay depends on the process of patients' recognition of the problem and their readiness to seek help.

The second type of delay is that caused by contacting a carer who is not a mental health professional. This delay depends on the time that carers take before they recognize a patient's problem or discover that their treatment of that problem was not successful, which makes them refer the patient to a mental health professional.

Our study showed that the delay between the onset of the symptom and contact to mental health professionals was the shortest among the patients who firstly accessed general hospitals (3 median weeks), compared with those among the patients who accessed private practitioners or directly accessed mental health professionals (8 median weeks, respectively). Patients tends to access general hospital or private practitioners more quickly than they access mental health professionals ($p < 0.1$). However, the advantage of early visit to the first carer is offset by the delay between the first carer and the mental health professionals; therefore total delay in this pathway becomes not significantly different among GH pathway, PP pathway and direct access. This is so for patients who did not improve under treatment by the non-mental health professionals, or were not immediately recognized as having a mental illness; all others - who reacted well to treatment or improved spontaneously - were better off having contacted general health facilities because they avoided stigmatization.

Physicians working in general hospitals refer their patients more quickly to mental health professionals than private practitioners. This may be because physicians in general hospitals are more specialized in their field of interest, which might enhance quicker referral compared with private practitioners, who are supposed to be more "general" in their practice. Compared with general hospital doctors, private practitioners are more likely to prescribe psychotropics and to give psychiatric diagnosis, although somewhat inappropriately.

The patients who presented somatic symptoms as their main problem experienced longer delay than patients who complained about psychiatric symptoms. This is similar to findings of studies in other countries. The reason for this finding may be that many such patients do not regard their problem as psychiatric symptoms and that they request their physician to carry out time-consuming physical examinations, and because physicians might think that they need to take their time for physical examinations to rule out physical illness.

Compared to patients with anxiety, patients with depressive symptoms are more likely to first seek care by contacting non-mental health professionals. Prior pathway studies suggest that psychotic feature lead to shorter

delays. Our study didn't support this, presumably due to small sample size.

Overall, patients access the first carer within a few weeks and then reach mental health professionals within one median week. These delays are as short as those in Spain[2], Cuba[2] and Turkey[9], and one of the shortest among pathway studies to date. This may be because at the number of psychiatrists per capita in Japan is much higher than those in countries in prior studies, as well as because patients are allowed to see any doctor or psychiatrist of their choice.

Compared with prior pathway studies, our study is unique in that we surveyed whether patients were told what their diagnosis was and explored care given to patients prior to the visit of mental health professionals. In our country, patients were rarely told their diagnosis and rarely received appropriate treatments from non-psychiatrists. Private practitioners were more likely to prescribe psychotropics compared with physicians in general hospitals, but were less likely to tell patients their diagnosis.

Our study has some limitations. First, small sample size makes it difficult to evaluate the effect of variation in diagnoses and characteristics of participating facilities. Second, participating centers were biased in their characteristics and locations. Psychiatric outpatient clinics (without wards) were not included in our study. The distribution of the diagnoses may have been influenced by unevenness in numbers and types of patients seen in the participating centers. Third, information gathered in this study is based on the willingness of patients to acknowledge their previous source of care. Thus, patients may have been reluctant to disclose contacts with carers (such as religious or traditional healers) or deny previous psychiatric treatment. Finally, as mentioned in previous reports, this study gives no account of those who do not reach mental health services.

Despite these limitations, this study is noteworthy in that this is the first multicenter study on pathway to psychiatric care in Japan. We hope that this study will generate hypotheses and studies focused on ways of improving the mental health care system in Japan.

Conclusion

The first pathway to psychiatric care study in Japan demonstrated that referral pathway in Japan heavily relies on medical resources. Approximately 40% of the patients directly access mental health professionals, another 40% via general hospital, and 15% via private practitioners. The study indicates importance of improving skills and knowledge that will facilitate the recognition of psychiatric

disorders presenting with somatic and depressive symptoms especially among private practitioners.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DF, NH and YMK had full access to the data and performed the statistical analysis. DF designed the study and drafted the manuscript. NH helped drafting the manuscript. KO managed the data. GO and MT participated in study design. AN conceived the study and participated in coordination of the study. RS, TK, ET, KY, TM, HT, SS, HI, YW, TU, IM were research directors of each participating center and played essential role in data acquisition. KT participated in data management. NS conceived the study, critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

This study was funded by a nonrestrictive grant from Pfizer Health Research Foundation. The authors express gratitude to Professor Y. Nakane in Nagasaki International University and Professor D. Goldberg in Institute of Psychiatry for their mentorship. We also thank members of JYPO for their support.

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Quantitative Analysis of NK₁ Receptor in the Human Brain Using PET with ¹⁸F-FE-SPA-RQ

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¹⁸F-fluoroethyl-SPA-RQ (¹⁸F-FE-SPA-RQ) was recently developed as a radioligand for the measurement of neurokinin 1 (NK₁) receptor with PET. In this study, we used ¹⁸F-FE-SPA-RQ with PET to visualize and quantify NK₁ receptor in the human brain. **Methods:** PET scans were performed on 7 healthy men after intravenous injection of ¹⁸F-FE-SPA-RQ. Binding potential (BP_{ND}) was calculated by the indirect kinetic, simplified reference tissue model (SRTM), and ratio methods. The indirect kinetic method was used as the gold standard method and was compared with the SRTM method, with scan times of 180, 270, and 330 min, and with the ratio method, with time integration intervals of 120–180, 210–270, and 300–330 min. The cerebellum was used as the reference brain region. **Results:** Regional radioactivity was highest in the caudate head and putamen; mid level in the parahippocampus, cerebral cortex, and thalamus; and lowest in the cerebellum. BP_{ND} values by the indirect kinetic method were 3.15 ± 0.36, 3.11 ± 0.66, 1.17 ± 0.25, and 0.46 ± 0.14 in the caudate, putamen, parahippocampal region, and thalamus, respectively. For cerebral cortical regions, BP_{ND} values by the indirect kinetic method were 0.94 ± 0.23, 0.82 ± 0.15, 0.76 ± 0.15, and 0.69 ± 0.16 in the occipital, temporal, frontal, and anterior cingulate cortices, respectively. BP_{ND} values by the SRTM and ratio methods were in good agreement with those by the indirect kinetic method ($r = 0.94$ – 0.98). **Conclusion:** The regional distribution of ¹⁸F-FE-SPA-RQ was in agreement with previous PET studies and postmortem studies of NK₁ receptor in the human brain. The ratio method will be useful for clinical research of psychiatric disorders, for the estimation of NK₁ receptor without arterial blood sampling and long dynamic PET.

Key Words: NK₁ receptor; substance P; ¹⁸F-FE-SPA-RQ; PET; human brain

J Nucl Med 2008; 49:1749–1755

DOI: 10.2967/jnumed.108.054353

Tachykinins are a family of neuropeptides that serve as neurotransmitters in the central nervous system (CNS) and peripheral nervous system (PNS). Three major mammalian

tachykinins—substance P (SP), neurokinin A, and neurokinin B—are known, and they share a consensus amino acid sequence (-Phe-X-Gly-Leu-Met-NH₂) in their carboxyl terminals (1–4). SP is a well-characterized neuropeptide, participating in neurotransmission by itself or synergistically with other neurotransmitters such as monoamines, acetylcholine, and glutamate in nerve terminals. Receptors for tachykinins—termed neurokinin 1 (NK₁), NK₂, and NK₃ receptors—have been identified (all are G protein-coupled 7-transmembrane receptors) and demonstrated to selectively show high affinity for SP, neurokinin A, and neurokinin B, respectively (5,6). NK₁ receptors are expressed in both CNS and PNS, whereas NK₂ and NK₃ receptors are expressed in PNS and CNS, respectively (7,8). SP and NK₁ receptors have been shown to play significant roles in pain (9), emesis (10), neuroinflammation (11,12), vasomotor control, and many gastrointestinal functions. Because the SP–NK₁ system is localized in brain regions (such as the striatum, amygdala, hypothalamus, raphe nucleus, and periaqueductal gray matter) that are involved in the regulation of affective behavior (7,8), the activity of the central tachykinergic pathway mediated by SP and NK₁ receptors is conceived to be mechanistically related to psychiatric conditions such as depression and anxiety disorder. Recent clinical trials of the NK₁ receptor antagonist aprepitant have shown that the blockade of SP is a highly effective strategy for the prevention of chemotherapy-induced nausea and vomiting (13–15). Aprepitant was recently registered worldwide, and it represents an improvement for antiemetic control during chemotherapy. Early clinical studies also suggested that aprepitant may have antidepressant activity, implicating SP in the modulation of mood and anxiety in humans (16,17). However, recent results from phase III clinical trials indicate that aprepitant is not effective for the treatment of depression (18).

A recently developed nonpeptide PET tracer that can permeate the blood–brain barrier, [¹⁸F-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2S,3S]2-phenylpiperidin-3-yl)-amine) (¹⁸F-SPA-RQ) (19), has been proven

Received May 14, 2008; revision accepted Jul. 14, 2008.

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