respectively, because sports-related motion is meaningful and goal-directed, whereas sports-unrelated motion itself could be meaningful biological motion but become non-meaningful and non-goal-directed in the context of sports game rules. For example, carrying the ball with a certain aim in daily life or in a certain sport (e.g. rugby) is a natural and goal-directed action, but becomes non-goal directed when accompanied by the aim to win a soccer game, because handling the ball is against the rules of soccer.

Although the issues regarding the precise role of EBA are still controversial,[15] recent studies have suggested an extended role for the EBA, involving not only static visual perception of body parts but also the planning, execution and imagination of actions,[16,17] and that the EBA is located at the entry of the human MNS.[17,18] We hypothesized that sports-related goal-directed motion would produce greater activation than sports-unrelated non-goal-directed motion in EBA along with STS and MNS.

METHODS

Participants

Twelve healthy volunteers (mean age 29.4 ± 4.5 years) participated in the present study. All subjects were Japanese and right-handed. All participants had played basketball in elementary or junior high school, but did not play basketball regularly thereafter. The participants were free of any criteria for neuropsychiatric disorders based on unstructured psychiatric screening interviews. None of the participants was taking 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 participants underwent magnetic resonance imaging to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all participants, and the study was approved by the Institutional Ethics Committee.

Materials

Two types of video clips were provided (basketball-related [BR] and basketball-unrelated [BU] motion). Examples of the video clips are shown in Fig. 1. Because a series of basketball plays consists of several actions and several players, it is difficult to provide a natural stream of control video clips (BU motion) consisting of identical numbers and directions of actions to BR motion. Therefore, we used some actions that are the components of a series of actions of a basketball game, aiming to make it easier to provide control actions (BU motion). BR motion consisted of three types of scenes (player shooting a free throw, player dribbling, two players performing man-to-man defense/offence). BU motion also consisted of three types of scenes (player rolling a basketball, player carrying a basketball, one player crossing in front of another without interaction). In order to make BR and BU motion as similar as possible, all players in the video clips performed in front of a basket goal on a basketball court, and the number of persons, objects, motion direction and speed were matched, that is, rolling a basketball, carrying a basketball, and crossing in front of another without interaction corresponded to shooting a free

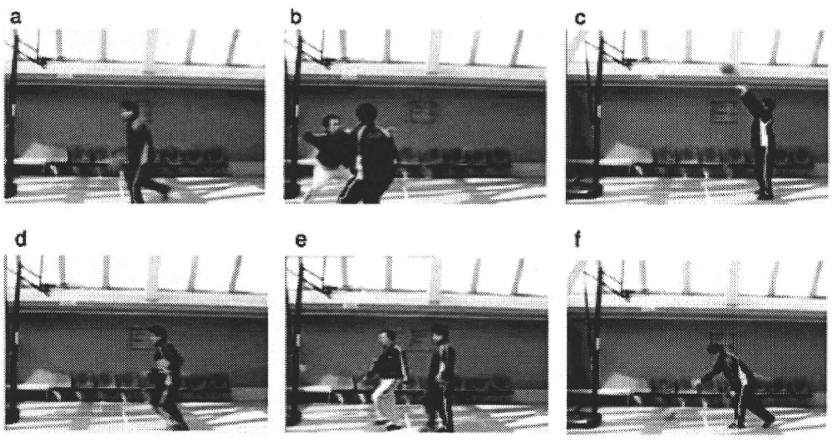

Figure 1. Sample of still frames from (a–c) basketball-related motions and (d–f) basketball-unrelated motions. (a) Dribbling; (b) man-to-man; (c) shooting; (d) carrying; (e) crossing; (f) rolling.

throw, dribbling, and man-to-man defense, respectively. The video clips were projected via computer and telephoto lens onto a screen mounted on a head-coil. The subjects were instructed to pay attention to the video clips and to press a selection button with the right index finger when they watched the free-throw scene and the basketball-rolling scene, indicating that they had paid attention to them. The experimental design consisted of five blocks for each of the two conditions (BR and BU motion) interleaved with 20-s rest periods. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In the BR and BU motion 24-s blocks, three scenes were presented twice for 4 s each. The order of BR and BU motion conditions was fixed across the subjects.

Image acquisition

Images were acquired with a 1.5-Tesla Signa system (General Electric, Milwaukee, WI, USA). Functional images of 115 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent (BOLD) contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; TE, 50 ms; TR, 4 s; matrix, 64 × 64; field of view, 24 × 24 cm). High-resolution, T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3-D spoiled gradient-recalled acquisition in a steady state sequence, slice thickness 1.5 mm, TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; field of view, 25 × 25 cm).

Analysis of functional imaging data

Data analysis was performed using a statistical parametric mapping software package (SPM02; Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA, USA). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute template. After normalization, all scans had a resolution of $2 \times 2 \times 2$ mm^3. Functional images were spatially smoothed with a 3-D isotropic Gaussian kernel (full width at half maximum, 8 mm). Low-frequency noise was removed by applying a high-pass filter (cut-off period, 192 s) to the functional MRI (fMRI) time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. Statistical parametric maps for each contrast of the *t*-statistic were calculated on a voxel-by-voxel basis.

To assess the specific condition effect, we used the contrasts of BR motion minus BU motion. A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization for the population from which data are obtained. Contrast images were obtained from single-subject analysis and entered into group analysis. A one-sample *t*-test was applied to determine group activation for each effect. A statistical threshold of $P < 0.05$ corrected for multiple comparisons across the whole-brain was used, except for a priori hypothesized regions thresholded at $P < 0.001$ uncorrected (only clusters involving ≥10 contiguous voxels are reported). These a priori regions of interest included the biological motion-related regions (STS, MT and EBA), human MNS (inferior parietal lobule [IPL] and inferior frontal cortex). We also assessed the contrasts of BU motion minus BR motion to investigate possible brain activations in response to the BU motion condition relative to BR motion condition.

RESULTS

Behavioral results

All subjects paid attention to the video clips and pressed the button appropriately (100% accuracy).

FMRI results

BR motion minus BU motion condition produced activations in the bilateral posterior temporal–occipital cortex including bilateral EBA ($x = 58$, $y = -60$, $z = 2$, $t = 4.86$) and MT ($x = 54$, $y = -66$, $z = -12$, $t = 8.38$), right STS ($x = 56$, $y = -22$, $z = -2$, $t = 6.58$), bilateral premotor cortex ($x = -48$, $y = -4$, $z = 40$, $t = 4.94$), and bilateral IPL ($x = -34$, $y = -50$, $z = 54$, $t = 7.25$; coordinates and t-score refer to the peak of each brain region; Fig. 2). A one-sample *t*-test of BU motion minus BR motion contrasts indicated no significant activation at a height threshold of

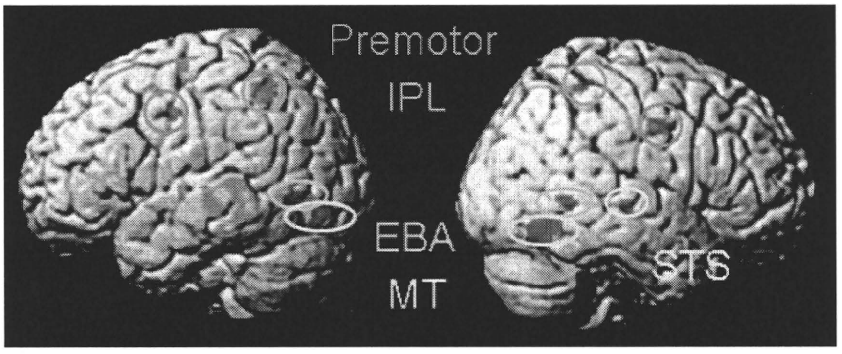

Figure 2. Brain activations in response to sports-related motion minus sports-unrelated motion. Significant activations in extrastriate body area (EBA), middle temporal (MT), superior temporal sulcus (STS), inferior parietal lobule (IPL) and premotor areas are shown. Within the images, L indicates left 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 was 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 motion[29] 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.

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Pathway to psychiatric care in Japan: a multicenter observational study

Daisuke Fujisawa*[1,2,3], Naoki Hashimoto[1,4], Yayoi Masamune-Koizumi[1,5], Kotaro Otsuka[1,6], Masaru Tateno[1,7], Gaku Okugawa[1,8], Atsuo Nakagawa[1,2,3], Ryoko Sato[1,9], Toshiaki Kikuchi[1,2,3], Eita Tonai[1,10], Kosuke Yoshida[1,10], Takatoshi Mori[1,11], Hidehiko Takahashi[1,12], Soichiro Sato[1,13], Hiroyasu Igimi[1,14], Yoshibumi Waseda[1,14], Takefumi Ueno[1,15], Ippei Morokuma[1,16], Katsuyoshi Takahashi[1,17] and Norman Sartorius[18]

Address: [1]Japan Young Psychiatrists Organization Pathway Study Group, 1-23-23-7F Ebisu, Shibuya-ku, Tokyo, Japan, [2]Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan, [3]Division of Psychiatry, Sakuragaoka Memorial Hospital, 1-1-1 Renkoji, Tama-shi, Tokyo, Japan, [4]Department of Psychiatry, School of Medicine, Hokkaido University, North15, West7, Sapporo, Japan, [5]Psychiatry Division, Kodama Hospital, 2-5-7 Shimomachi, Ishinomaki, Miyagi, Japan, [6]Department of Neuropsychiatry, Iwate Medical University, 19-1 Uchimaru, Morioka-shi, Iwate, Japan, [7]Division of Neuropsychiatry, Sapporo Medical University, South 1, West16, Chuo-ku, Sapporo, Hokkaido, Japan, [8]Department of Neuropsychiatry, Kansai Medical School,10-15 Fumizonomachi, Moriguchi-shi, Osaka, Japan, [9]Department of Psychiatry, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa, Japan, [10]Department of Psychiatry, School of Medicine Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, Japan, [11]Division of Psychiatry, Takagi Hospital, 1165 Nakanomachihei, Shimabara-shi, Nagasaki, Japan, [12]National Institute of Radiological Sciences, 4-9-1 Anakawa, Inage-ku, Chiba, Japan, [13]Division of Psychiatry, Zikei Hospital, 100-2 Urayasuhonmachi, Okayama-shi, Okayama, Japan, [14]Department of Neuropsychiatry, Kurume University School of Medicine, 281 Shiromaru Oaza Buzen-shi, Fukuoka, Japan, [15]Department of Neuropsychiatry, Kyushu University Graduate School of Medical Sciences, 3-1-1, Maidashi, Higashi-ku, Fukuoka, Japan, [16]Department of Psychiatry, Kochi University School of Medicine, Kohasu, Okatoyocho, Nangoku-shi, Kochi, Japan, [17]Division of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, 2-1-1 Kamikitazawa, Setagaya-ku, Tokyo, Japan and [18]Department of Psychiatry, Geneva University, Department de Psychiatrie, 16-18, Bd de St Georges, 1205 Geneva, Switzerland

Email: Daisuke Fujisawa* - fujisawa@sc.itc.keio.ac.jp; Naoki Hashimoto - hashinao@vega.ocn.ne.jp; Yayoi Masamune-Koizumi - aglaia-thk@umin.ac.jp; Kotaro Otsuka - Kotaro29@df6.so-net.ne.jp; Masaru Tateno - tatema@sapmed.ac.jp; Gaku Okugawa - okugawa@takii.kmu.ac.jp; Atsuo Nakagawa - nakagawa@keio-psychiatry.com; Ryoko Sato - rykst@mcn.ne.jp; Toshiaki Kikuchi - t-kick@nifty.com; Eita Tonai - eita.tonai@mbj.nifty.com; Kosuke Yoshida - EZZ04613@nifty.ne.jp; Takatoshi Mori - woods@vega.ocn.ne.jp; Hidehiko Takahashi - hidehiko@nirs.go.jp; Soichiro Sato - soichiro@ja2.so-net.ne.jp; Hiroyasu Igimi - igimi@k2.dion.ne.jp; Yoshibumi Waseda - wyalfa@yahoo.co.jp; Takefumi Ueno - uenotk@gmail.com; Ippei Morokuma - morokuma@kochi-u.ac.jp; Katsuyoshi Takahashi - k2t91057@s2.ocv.ne.jp; Norman Sartorius - Sartorius@normansartorius.com

* Corresponding author

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

Main problem presented and diagnosis given by mental healthprofessionals

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

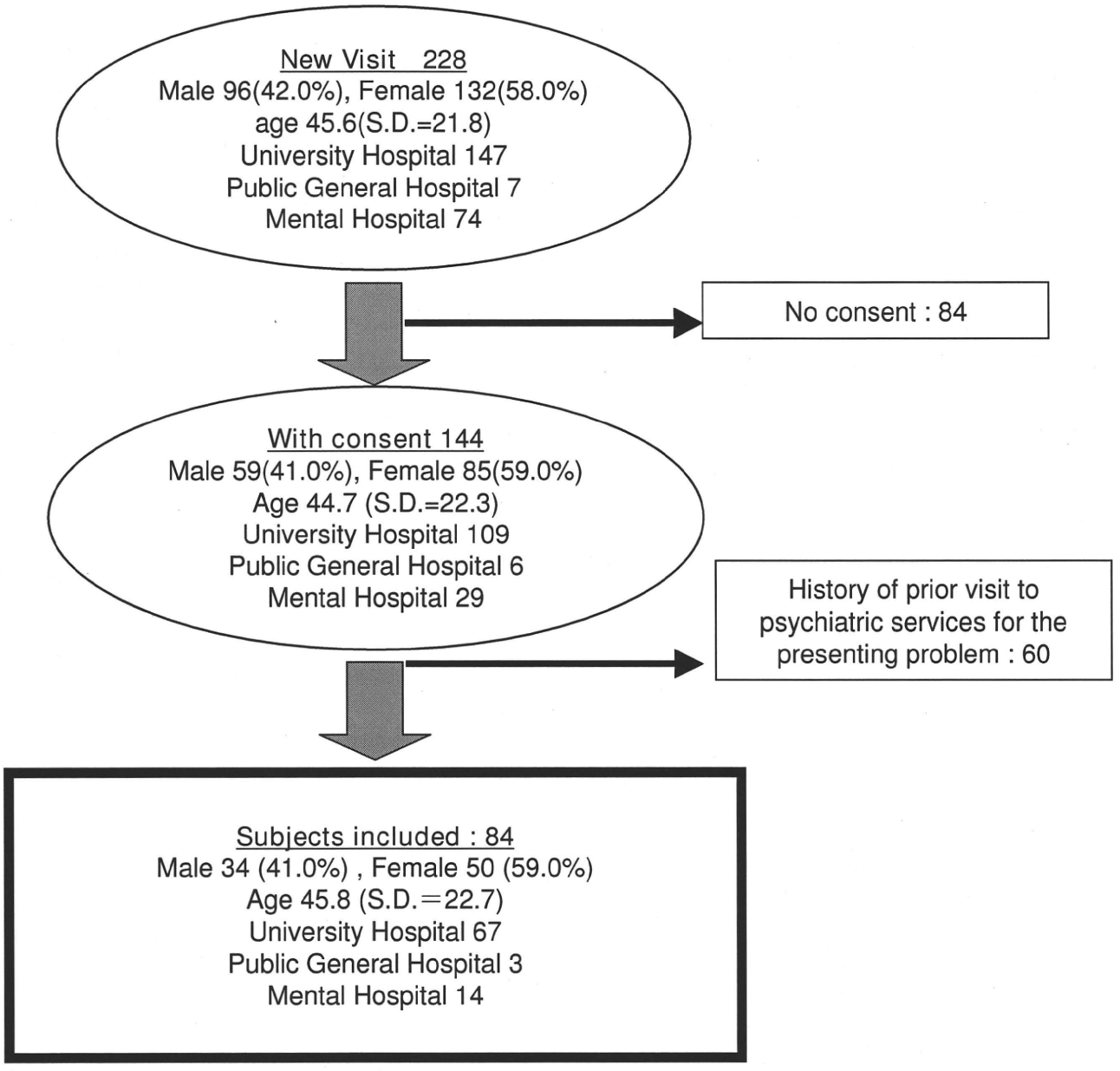

Figure 1
Inclusion procedure and demographics of the subjects. Figure legend text.

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

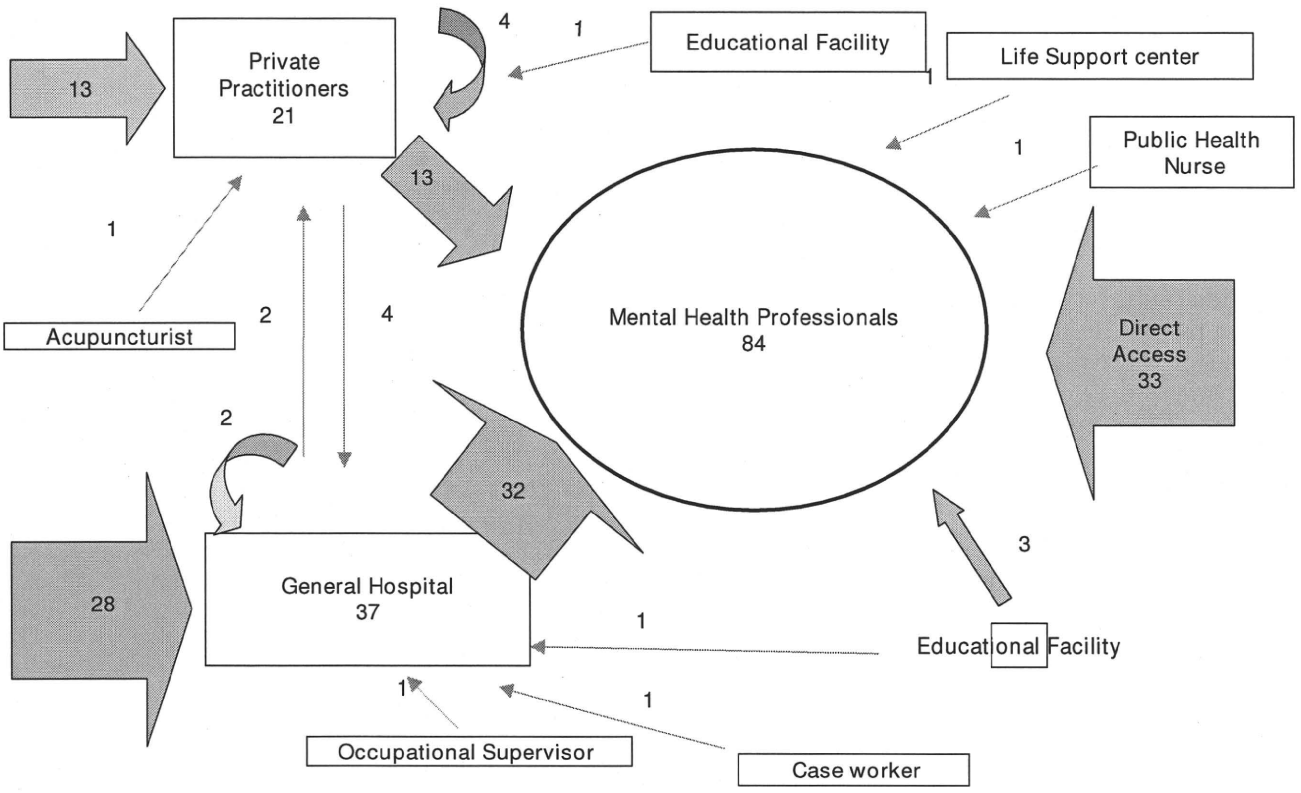

Figure 2
The Pathway Diagram. Figures indicate numbers of subjects who took each pathway or consulted each carer. Curved arrows indicate recursive pathways, where patients have gone from one to another of the same type of carer.

hospital doctors than by private practitioners. Only to 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 extract 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

				Psychiatric diagnosis		Treatment		
	Number of patients	Patients who visited MHPs as the next step	Patients referred to MHPs by prior carers	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 extract 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.

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$GABA_A$/Benzodiazepine receptor binding in patients with schizophrenia using [^{11}C]Ro15-4513, a radioligand with relatively high affinity for α5 subunit

Yoshiyuki Asai [a,b,c], Akihiro Takano [a], Hiroshi Ito [a], Yoshiro Okubo [d], Masato Matsuura [e], Akihiko Otsuka [f], Hidehiko Takahashi [a], Tomomichi Ando [a,g], Shigeo Ito [a], Ryosuke Arakawa [a], Kunihiko Asai [c], Tetsuya Suhara [a,*]

[a] *Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba, 263-8555, Japan*
[b] *Department of Psychiatry, Division of Neurological Science, Hokkaido University Graduate School of Medicine, Sapporo, Japan*
[c] *Asai Hospital, Togane, Japan*
[d] *Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan*
[e] *Biofunctional Informatics, Department of Life Sciences and Bio-informatics, Division of Biomedical Laboratory Sciences, Graduated School of Health Sciences, Tokyo Medical and Dental University, Japan*
[f] *Otsuka Clinic, Chiba, Japan*
[g] *Sobu Hospital, Funabashi, Japan*

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Abstract

Dysfunction of the GABA system is considered to play a role in the pathology of schizophrenia. Individual subunits of $GABA_A$/Benzodiazepine (BZ) receptor complex have been revealed to have different functional properties. α5 subunit was reported to be related to learning and memory. Changes of α5 subunit in schizophrenia were reported in postmortem studies, but the results were inconsistent. In this study, we examined $GABA_A$/BZ receptor using [^{11}C]Ro15-4513, which has relatively high affinity for α5 subunit, and its relation to clinical symptoms in patients with schizophrenia.

[^{11}C]Ro15-4513 bindings of 11 patients with schizophrenia (6 drug-naïve and 5 drug-free) were compared with those of 12 age-matched healthy control subjects using positron emission tomography. Symptoms were assessed using the Positive and Negative Syndrome Scale. [^{11}C]Ro15-4513 binding was quantified by binding potential (BP) obtained by the reference tissue model. [^{11}C]Ro15-4513 binding in the prefrontal cortex and hippocampus was negatively correlated with negative symptom scores in patients with schizophrenia, although there was no significant difference in BP between patients and controls. $GABA_A$/BZ receptor including α5 subunit in the prefrontal cortex and hippocampus might be involved in the pathophysiology of negative symptoms of schizophrenia.

Keywords: γ-Amino-butyric acid; Schizophrenia; Negative symptoms; Prefrontal cortex; Hippocampus; PET

1. Introduction

γ-Amino-butyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system.

* Corresponding author. Tel.: +81 43 206 3250; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

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$GABA_A$/Benzodiazepine (BZ) receptors are heteropentamiric GABA-gated chloride channels, and mediate fast synaptic inhibition (Moss and Smart, 2001). Benzodiazepines enhance the action of the neurotransmitter GABA at $GABA_A$/BZ receptors by interaction with their modulatory benzodiazepine sites.

Dysfunction of GABA neurotransmission in the brain is thought to play a role in the pathology of schizophrenia (Simpson et al., 1989; Reynolds et al., 1990). Postmortem studies using [^{3}H]muscimol showed that binding was increased in the hippocampal formation (Benes et al., 1996a), anterior cingulate cortex (Benes et al., 1992) and prefrontal cortex (Benes et al., 1996b; Dean et al., 1999) in patients with schizophrenia. The axon terminals of chandelier GABA neurons are reported to be reduced substantially in the middle layers of the prefrontal cortex in schizophrenia (Lewis et al., 1999).

$GABA_A$/BZ receptor chloride channel complex consists of two α subunits, two β subunits and one γ subunit (Barnard et al., 1998; Lüddens et al., 1995; Mehta and Ticku, 1999). It has been reported that the diversity of α subunits is responsible for various functional properties and ligand selectivity to the $GABA_A$/BZ receptor (Barnard et al., 1998; Low et al., 2000; Mehta and Ticku, 1999; Tobler et al., 2001). α1 subunit has been suggested to be related to hypnotic and sedative amnesic actions, whereas α2, α3 and α5 subunits to anxiolytic, anticonvulsant, and antipsychotic actions, and to the function of learning and memory (Crestani et al., 2001; Mohler et al., 2001; Serwanski et al., 2006).

Alterations in individual subunits of $GABA_A$/BZ receptor in schizophrenia have been the focus of recent postmortem studies. Expression of α1 subunit was reported to increase in the prefrontal cortex of patients with schizophrenia (Ohnuma et al., 1999; Ishikawa et al., 2004), α2 subunit was reported to increase in the prefrontal cortex (Volk et al., 2002), and α5 subunit expression was reported to show no significant change (Akbarian et al., 1995) or increase (Impagnatiello et al., 1998).

Several ligands such as [^{11}C]flumazenil and [^{11}C]Ro15-4513 were developed to visualize $GABA_A$/BZ receptors by positron emission tomography (PET) (Inoue et al., 1992; Halldin et al., 1992; Pappata et al., 1988). Both [^{11}C]flumazenil and [^{11}C]Ro15-4513 have the imidazobenzodiazepine core structure. However, flumazenil is a $GABA_A$/BZ receptor antagonist while Ro15-4513 is known as a $GABA_A$/BZ receptor partial inverse agonist. A different distribution pattern has been reported for the binding of [^{11}C]Ro15-4513 compared to that of [^{11}C]flumazenil (Inoue et al., 1992; Halldin et al., 1992). Ro15-4513 was reported to have relatively higher affinity for the α5 subunit-containing $GABA_A$/BZ receptor *in vitro* (Lüddens et al., 1994; Wieland and Lüddens, 1994). [^{11}C]Ro15-4513 bindings in the cingulate and temporal cortical regions showed relatively higher binding to α5 subunit of $GABA_A$ receptor (Lingford-Hughes et al., 2002; Maeda et al., 2003).

A simplified method without arterial blood sampling for [^{11}C]Ro15-4513 in the living human brain has been evaluated recently, and it can be used in clinical studies (Asai et al., in press).

In this study, we measured [^{11}C]Ro15-4513 binding to examine $GABA_A$/BZ receptors with α5 subunit and their relation to clinical symptoms in patients with schizophrenia.

2. Methods and materials

2.1. Subjects

Eleven patients with schizophrenia (5 women, 6 men; 32.8±10.2 years old, mean±SD) meeting DSM-IV criteria for schizophrenia or schizophreniform disorder were enrolled in this study. Demographic and clinical data on subjects are shown in Table 1. Six of the patients (3 women, 3 men; 29.2±7.3 years old) were neuroleptic-naïve and five (2 women, 3 men; 37.2±12.2 years old) had been neuroleptic-free for at least one year before the PET measurement except one subject who took

Table 1
Demographic and clinical characteristics asstudy entry

						PANSS			
	N	Age (years)	Male/ female	Duration of illness (months)	Schizophrenia/ schizophreniform	Positive	Negative	General	Total
Patient	11	32.8±10.2	6/5	1–444	9/3	24.4±5.1	21.4±6.0	44.6±10.2	90.4±19.6
Drug-naïve	6	29.2±7.3	3/3	1–36	3/3	24.8±3.9	20.3±8.0	45.3±12.0	90.5±23.0
Drug-free	5	37.2±12.2	3/2	24–444	6/0	23.8±6.8	22.6±2.5	43.8±8.8	90.2±17.4
Normal controls	12	29.0±10.2	12/0	–	–	–	–	–	–

neuroleptics two weeks before the PET measurement. Three neuroleptic-naïve patients satisfying criteria for schizophreniform disorder (duration of illness 1 to 4 months at the time of PET measurement) met criteria for schizophrenia at 6-month follow-up. The patients were recruited from the outpatient units of university-affiliated psychiatric hospitals, psychiatric divisions of general hospitals, and a mental clinic in the urban environments of Tokyo and Chiba prefectures in Japan. Exclusion criteria were current or past substance or cannabis or alcohol abuse, mood disorders, organic brain disease, and medication of antipsychotics, antidepressants, or benzodiazepines or mood stabilizers within two weeks before PET measurement. Five out of 11 subjects were smokers.

Psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). PANSS was completed by three experienced psychiatrists on the same day as PET measurements was performed. They reviewed the ratings after the interviews, and disagreements were resolved by consensus; the consensus ratings were used in this study. The symptom scores were calculated as the total scores, positive symptom, negative symptom, and general symptom subscores of PANSS. The total PANSS score ranged from 60 to 124 (90.4±19.6, mean±SD), mean positive symptom scores were 24.4±5.1, negative symptom scores were 21.4±6.0, and general symptom scores were 44.6±10.2.

Normal control subjects (12 men, 29.0±10.2 years old) were recruited through notices on bulletin boards at the universities and among the staffs of the affiliated hospitals where the patients had been diagnosed. None of the controls had a history of psychiatric or neurological illness, brain injury, chronic somatic illness, or substance abuse. None had taken any drug including benzodiazepines within two weeks before PET measurements. Seven out of 12 subjects were smokers. All the subjects were examined by T1-weighted magnetic resonance image (MRI) using 1.5 T Philips Gyroscan NT to rule out organic brain diseases. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from all subjects.

2.2. PET measurement

[^{11}C]Ro15-4513 was synthesized by *N*-methylation of a corresponding *N*-desmethyl precursor with [^{11}C] methyl iodide. The reaction mixtures were purified by liquid chromatography, eluted with CH_3CN/6mM-phosphoric acid=175/325. The radiochemical purities were more than 95%.

The PET system used was ECAT EXACT HR+(CTI-Siemens, Knoxville, TN, USA), which provides 63 planes and a 15.5-cm field of view and was used in 3-dimensional mode. After a 10-minute transmission scan, a bolus of 352.3±66.9 MBq (mean±SD) of [^{11}C] Ro15-4513 with high specific radioactivities (103.4±38.9 GBq/μmol; mean±SD) was injected into the antecubital vein with a 20-ml saline flush. Radioactivity in the brain was measured in a series of sequential frames up to 60 min (total 28 frames).

2.3. PET data analysis

All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (FWHM 7.5 mm). Regions-of-interest (ROIs) were delineated on PET/MRI coregistered images for ten target regions (anterior cingulate, hippocampus, amygdala, thalamus, temporal cortex, prefrontal cortex, insula, caudate, putamen, cerebellum) and the pons as a reference region. Regional binding potentials were calculated using a simplified reference tissue model (SRTM)(Lammertsma and Hume, 1996). In brief, based on the three-compartment model, regional radioactivities in a target region (C_T) can be described by the following equation:

$$C_T(t) = R_1 C_R(t) + (k_2 - R_1\theta_3) C_R(t) * e^{-\theta_3 t},$$

where C_R represents the radioactivity in the reference region, R_1 is the ratio of K_1 in a target region to the reference region, $\theta_3 = k_2/(1+BP)$, K_1 and k_2 are rate constants corresponding to the influx and efflux rates from plasma to the tissue compartments, and * is the

Table 2
Binding potentials for regions of interest

	BP values		*T* test (df=21)	
	Controls (*N*=12)	Patients (*N*=11)	*T* score	*p*
Anterior cingulated	6.08±0.72	6.14±0.63	−0.213	0.833
Hippocampus	5.43±0.77	4.95±0.80	1.432	0.167
Amygdala	5.49±0.56	5.25±0.48	1.118	0.276
Thalamus	2.00±0.28	1.83±0.24	1.534	0.14
Temporal cortex	4.20±0.52	4.12±0.38	0.438	0.666
Prefrontal cortex	3.60±0.35	3.59±0.34	0.09	0.929
Insula	5.79±0.63	5.56±0.46	1.011	0.324
Caudate	2.99±0.43	3.32±0.81	−1.199	0.249
Putamen	2.86±0.36	3.10±0.45	−1.445	0.165
Cerebellum	1.32±0.25	1.34±0.23	0.148	0.883

Values are mean±SD.

convolution operator. In this study, the pons was chosen as the reference tissue because this region is almost devoid of $GABA_A$/BZ receptor complex (Abadie et al., 1992).

2.4. Statistical analysis

Statistical analysis of the difference of regional BP or R_1 for each ROI between patients and controls was performed by repeated measures analysis of variance (ANOVA). When any interaction was found, post hoc Bonferroni correction was used for multiple comparisons. $p<0.05$ was considered significant.

Correlations between regional BP and PANSS scores were analyzed with Pearson's correlation method. $p<0.05$ was considered significant.

3. Results

Regarding regional BP values of [^{11}C]Ro15-4513, two-way repeated ANOVA revealed significant group-region interaction [$F_{4.3,90.6}=2.6$, $p=0.037$]. However, post hoc Bonferroni correction showed no significant differences of BPs for 10 ROIs between patients and controls (Table 2). As for R_1 values, two-way repeated ANOVA revealed no significant main effect of the groups [$F_{4.9,103.9}=1.613$, $p=0.164$] nor group-region interaction [$F_{1,21}=1.532$, $p=0.229$].

For the reference tissue, time activity curves of the pons between patients with schizophrenia and controls were compared with repeated-measures ANOVA with Green–Geisser correction. There was no significant main effect of groups [$F_{1,21}=1.027$, $p=0.323$] or no significant group by time interaction [$F_{2.09,43.9}=0.203$, $p=0.826$].

Regarding the relation to clinical symptoms, there were significant negative correlations between [^{11}C] Ro15-4513 binding in the prefrontal cortex and negative symptom scores ($R=-0.733, p=0.010$)(Fig. 1A), general symptom scores ($R=-0.655$, $p=0.029$) (Fig. 1C), and total PANSS scores ($R=-0.690$, $p=0.019$) (Fig. 1D). There was also a negative correlation between [^{11}C]Ro15-4513 binding in the hippocampus and negative symptom scores ($R=-0.605, p=0.048$) (Fig. 1B). No other regions

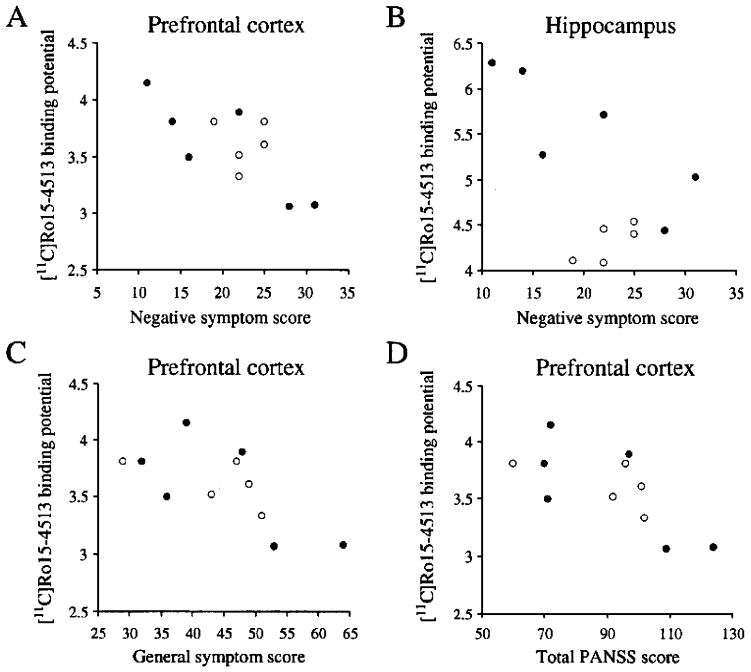

Fig. 1. Relationship between regional [^{11}C]Ro15-4513 binding potentials and PANSS scores in 11 patients with schizophrenia. Filled circles indicate neuroleptic-naïve patients ($N=6$). Open circles indicate drug-free patients ($N=5$). Total PANSS scores consist of positive symptom scores, negative symptom scores, and total symptom scores. There were significant negative correlations between [^{11}C]Ro15-4513 binding in the prefrontal cortex and negative symptom scores ($R=-0.733$, $p=0.010$)(A), general symptom scores ($R=-0.655$, $p=0.029$) (C), and total PANSS scores ($R=-0.690$, $p=0.019$) (D). There was also a negative correlation between [^{11}C]Ro15-4513 binding in the hippocampus and negative symptom scores ($R=-0.605$, $p=0.048$) (B).

Table 3
Correlation between regional [11C]Ro15-4513 binding potentials and PANSS scores

	Positive symptoms		Negative symptoms		General symptoms		Total scores	
Region	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*
Anterior cingulate	−0.123	0.718	−0.312	0.350	−0.079	0.817	−0.169	0.620
Hippocampus	−0.008	0.982	−0.605	0.048*	−0.221	0.513	−0.302	0.367
Amygdale	−0.394	0.231	−0.307	0.359	−0.282	0.401	−0.343	0.302
Thalamus	−0.298	0.373	−0.163	0.633	0.005	0.987	−0.125	0.714
Temporal cortex	−0.415	0.205	−0.594	0.054	−0.564	0.070	−0.583	0.060
Prefrontal cortex	−0.485	0.131	−0.733	0.010*	−0.655	0.029*	−0.690	0.019*
Insula	−0.146	0.668	−0.541	0.085	−0.281	0.403	−0.349	0.292
Caudate	−0.164	0.630	−0.118	0.729	0.031	0.929	−0.063	0.854
Putamen	−0.383	0.245	−0.287	0.393	−0.184	0.587	−0.283	0.398
Cerebellum	0.057	0.868	−0.120	0.725	−0.010	0.976	−0.027	−0.937

showed significant correlation with clinical symptom scores (Table 3).

4. Discussion

In this study, significant negative correlation between clinical symptoms (especially negative symptoms) and $GABA_A$/BZ receptor binding in the prefrontal cortex (Fig. 1A, C, D) and the hippocampus (Fig. 1B) of the patients with schizophrenia was found. The significant relation between $GABA_A$/BZ receptor binding and clinical symptoms would suggest dysfunctions of the GABA system in schizophrenia.

Our results showed no significant difference of $GABA_A$/BZ receptor binding between patients with schizophrenia and controls (Table 2). This is consistent with some of the previous postmortem studies (Akbarian et al., 1995; Impagnatiello et al., 1998). However, inconsistent results have also been reported (Benes et al., 1996a, 1996b; Dean et al., 1999). Inconsistency can be attributed to methodological differences between PET study and postmortem study, as well as to the effects of prolonged antipsychotic and benzodiazepine administration. None of the patients in this study had taken any antipsychotics or benzodiazepines for at least two weeks before PET measurement. On the other hand, most of the subjects investigated in the postmortem studies had taken antipsychotics and/or benzodiazepines on a long-term basis. Recently, it was suggested from an animal experiment that antipsychotic drug administration would result in a "reshuffling" of $GABA_A$ receptor subtypes (Skilbeck et al., 2007).

Although there was no significant difference in [^{11}C] Ro15-4513 binding between patients and controls, [^{11}C] Ro15-4513 binding was found to be negatively correlated with clinical symptom scores. Although some previous SPECT studies using [^{123}I]iomazenil showed no significant difference of benzodiazepine binding between patients and controls (Abi-Dargham et al., 1999, Verhoeff et al., 1999), some reported that there were significant negative correlations between benzodiazepine binding and the severity of negative symptoms (Busatto et al., 1997), or cognitive impairment (Ball et al., 1998) in patients with schizophrenia. Our results were consistent with those studies, despite [^{11}C]Ro15-4513 having relatively high affinity for α5 subunit of $GABA_A$/BZ receptor while [^{123}I]iomazenil binds to $GABA_A$/BZ receptor non-selectively.

α5 subunit-containing $GABA_A$ receptors are reported to be concentrated in the apical dendrites of pyramidal neurons (Akbarian et al., 1995). In a postmortem study, α2 subunit of GABA in the axonal initial segment of pyramidal neurons was reported to be increased in patients with schizophrenia (Volk et al., 2002). The expression of subunits of $GABA_A$/BZ receptor was reported to be changed following chronic administration of phencyclidine, which induces schizophrenia-like symptoms in rats (Abe et al., 2000). Combining our results with these reports, the imbalance among α subunits in pyramidal neurons could be expected in patients with schizophrenia.

Dopamine receptors in the prefrontal cortex have been suggested to be involved in the pathophysiology of schizophrenia. Dopamine D1 receptor plays a key role in negative symptoms and cognitive dysfunctions of schizophrenia (Abi-Dargham et al., 2002; Okubo et al., 1997). Reduced prefrontal pyramidal neuron output could change the activity of dopamine neurons in the prefrontal cortex in schizophrenia (Lewis and Gonzalez-Burgos, 2006). The possible change of α5 subunit in the prefrontal cortex might cause the change of pyramidal neuron output, which might interact with dopamine D1 receptor.

Not only the prefrontal cortex but also the hippocampus was found to be correlated negatively with negative symptoms of patients with schizophrenia in this study (Fig. 1B). Hippocampal-dependent spatial learning was improved in α5 subunit of $GABA_A$ receptor-knockout mice (Collinson et al., 2002), or by systemic treatment of an inverse agonist selective for α5 $GABA_A$ receptors (Chambers et al., 2003). The change of α5 subunit of $GABA_A$ receptors in the prefrontal cortex in patients with schizophrenia might affect hippocampal function because of the plastic neuronal connections between the hippocampus and prefrontal cortex (Goldman-Rakic et al., 1984; Laroche et al., 2000; Maccotta et al., 2007; Tierney et al., 2004; Takahashi et al., 2007).

There has been some interest in treating negative symptoms and cognitive dysfunctions in schizophrenia with GABA-modulating drugs (Guidotti et al., 2005; Lewis et al., 2004; Menzies et al., 2007). Imidazenil, which selectively allosterically modulates cortical $GABA_A$ receptors containing α5 subunit, was reported to contribute to amelioration of the behavioral deficits without producing sedation or tolerance liability in mice (Guidotti et al., 2005), and it increased locomotor activity in a social isolation mouse model (Pinna et al., 2006).

There were several limitations to this preliminary study. The number of subjects was small, and five of the eleven patients were previously treated. Further study would be needed with a larger population of drug-naïve patients. Although age correction was not performed, we previously reported no significant age effect of [^{11}C] Ro15-4513 binding (Suhara et al., 1993). We also compared with age-matched subgroup of drug naïve paitents (N=6) with controls (N=12) and two-way repeated ANOVA revealed no significant group-region interaction of [^{11}C]Ro15-4513 binding.

Sex was not matched between patients and controls, but sex differences of [^{11}C]Ro15-4513 binding have not been reported.

In conclusion, the present study showed that [^{11}C] Ro15-4513 binding was negatively correlated with negative symptom scores in schizophrenia. $GABA_A$/BZ receptor including α5 subunit might be involved in the pathophysiology of schizophrenia with negative symptoms.

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Contributors

Y Asai, T Takano and T Suhara designed the study and wrote the protocol. Y Okubo, M Matsuura, A Otsuka, H Takahashi, T Ando, and S Ito recruited the subjects and made psychiatric evaluations. Y Asai, T Takano, and R Arakawa performed the data analysis. Y Asai wrote the first draft of the manuscript. H Ito gave fruitful comments to finalize the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors have no conflict of interest.

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