International Journal of Neuropsychopharmacology, Page 1 of 5. Copyright © 2007 CINP
doi:10.1017/S1461145707008103

BRIEF REPORT

CINP

Enhanced dopamine release by nicotine in cigarette smokers: a double-blind, randomized, placebo-controlled pilot study

Hidehiko Takahashi[1], Yota Fujimura[1], Mika Hayashi[2], Harumasa Takano[1], Motoichiro Kato[2], Yoshiro Okubo[3], Iwao Kanno[1], Hiroshi Ito[1] and Tetsuya Suhara[1]

[1] *Molecular Imaging Centre, Department of Molecular Neuroimaging, National Institute of Radiological Sciences, Anagawa, Inage-ku, Chiba, Japan*

[2] *Department of Neuropsychiatry, Keio University School of Medicine, Shinanomachi, Shinjuku-ku, Tokyo, Japan*

[3] *Department of Neuropsychiatry, Nippon Medical School, Sendagi, Bunkyo-ku, Tokyo, Japan*

Abstract

Previous studies of smoking on dopamine release in humans were investigated only in smokers. Using nicotine gum, we examined the effect of nicotine on dopamine release in smokers and non-smokers and its relation to the degree of nicotine dependence. Smokers and non-smokers participated in a double-blind, randomized, placebo-controlled cross-over study. They participated in two PET measurements with [^{11}C]raclopride, in which they received either nicotine or placebo. Changes in [^{11}C]raclopride non-displaceable binding potential (BP_{ND}) following nicotine administration were quantified. Smokers showed significant decrease in BP in the striatum following nicotine administration, but non-smokers did not show such a decrease. The BP_{ND} difference between the two scanning sessions was correlated with the degree of nicotine dependence. The BP_{ND} difference might reflect enhanced dopamine release in smokers and the reinforced effect of nicotine. These data suggest the feasibility of our gum method as well as the importance of the degree of dependence in future studies of the nicotine effect on the dopamine system.

Received 15 May 2007; Reviewed 4 July 2007; Revised 18 August 2007; Accepted 25 August 2007

Key words: Dependence, dopamine, nicotine, positron emission tomography, striatum.

Introduction

Nicotine is a major psychostimulant component of tobacco. Repeated nicotine exposure can induce nicotine dependence (Laviolette and van der Kooy, 2004; Olausson et al., 2003). It has been suggested that the mesolimbic dopamine pathway is involved in nicotine dependence (Yasuno et al., 2007). [^{11}C]raclopride has been used for the indirect measurement of changes in synaptic dopamine concentration in vivo using PET in response to addictive drugs like cocaine and amphetamine (Dewey et al., 1993). Dopamine is thought to compete with [^{11}C]raclopride at the D_2 receptor, and dopamine release is associated with a reduction in [^{11}C]raclopride binding (Dewey et al., 1993). Decreases in [^{11}C]raclopride binding potential (BP) in the ventral striatum have been demonstrated in smokers following cigarette smoking (Brody et al., 2004, 2006; Scott et al., 2007). On the other hand, two human PET studies of smokers (Barrett et al., 2004; Montgomery et al., 2007) and an awake-monkey study (Tsukada et al., 2002) showed no overall changes in [^{11}C]raclopride BP after exposure to nicotine. However, the monkeys were nicotine-naive, and the study by Montgomery et al. mainly examined low-dependence smokers. It can be expected that the degree of nicotine dependence affects dopamine release in the brain (Scott et al., 2007). In this study, we used nicotine gum with the aim of exposing non-smokers to nicotine to the same degree as smokers. Another objective of this pilot study was to examine the feasibility of nicotine gum methods. The study was conducted in a double-blind, randomized, placebo-controlled manner.

Address for correspondence: T. Suhara, M.D., Ph.D., Molecular Imaging Centre, Department of Molecular Neuroimaging, National Institute of Radiological Sciences, 9-1, 4-chome, Anagawa, Inage-ku, Chiba, Chiba 263-8555, Japan.
Tel.: +81-43-206-3194 *Fax*: +81-43-253-0396
E-mail: suhara@nirs.go.jp

Method

Participants

Twelve male subjects (six smokers, mean age 25.8 ± 2.6 yr, and six non-smokers, 23.7 ± 2.7 yr) participated in a double-blind, randomized, placebo-controlled, cross-over pilot study. Smokers had a smoking history of at least 4 yr, with current use of ⩾15 cigarettes per day. The Fagerstrom test for nicotine dependence (FTND) was applied (Heatherton et al., 1991). The FTND, consisting of six questions (e.g. How soon after you wake up do you smoke your first cigarette? How many cigarettes per day do you smoke?), yields a score ranging from 0 to 10 (0–2, very low dependence; 8–10 very high dependence). The non-smokers had no history of recreational use of cigarettes. None of the subjects were 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 (other than nicotine) dependence. MRI demonstrated intact cerebral structures in all subjects. All subjects were right-handed according to the Edinburgh Handedness Inventory. Smokers were instructed not to smoke for 24 h before scanning, and abstinence was verified by plasma nicotine measurement. Both before and after the administration of nicotine, the strength of cigarette craving was assessed using a 6-point scale (0 = no urge, 5 = extremely strong urge). After description of the study to the subjects, written informed consent was obtained, and the study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Japan.

Nicotine administration

Each subject participated in two PET sessions. To ensure maximum and stable plasma concentrations of nicotine during the PET scans, 1 h before each scan the subjects received two pieces of either nicotine (2 mg Nicorette, mint taste; Pfizer, Tokyo, Japan) or taste-matched placebo gum. A clinical research coordinator (Y.F.), generated the randomization sequence (the order of the two sessions) and packaged the placebo and nicotine gum in containers according to the balanced randomization list (half of the subjects took nicotine gum first, and the remaining half took placebo gum first). The participants and all study staff and investigators, except Y.F., remained blinded to the treatment allocation throughout the study. Every 3 min, the subjects chewed the gum five times at a rate of 1 Hz and then put the gum into the oral vestibule in front of the lower anterior teeth. Until the start of the PET scans, the subjects were trained to chew the gum while not moving the maxilla but moving only the mandible in order to minimize head motion associated with jaw motion during mastication. The participants kept chewing the gum in the same way during the scans, and finally finished chewing at the end of the scans. Blood samples for measurement of plasma nicotine concentration were collected just before gum administration, and at 60 min, 75 min, 90 min, 105 min, and 120 min after gum administration.

PET scan

PET studies were performed on ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA). The system provides 63 planes and a 15.5-cm field of view. To minimize head movement, a head fixation device (Fixster, Stockholm, Sweden) was used. A transmission scan for attenuation correction was performed using a germanium-68–gallium-68 source. Acquisitions were performed in 3D mode with the interplane septa retracted. A bolus of 225.1 ± 9.7 MBq of [^{11}C]raclopride with a specific radioactivity of 262.0 ± 97.6 GBq/μmol was injected intravenously from the antecubital vein with a 20-ml saline flush. Dynamic scans were performed for 60 min immediately after the injection. All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (full width at half maximum, 7.5 mm). MRI was performed on Gyroscan NT (Philips Medical Systems, Best, The Netherlands) (1.5 T). T1-weighted brain images were obtained for all subjects. The scan parameters were 1-mm-thick, 3D T1 images with a transverse plane (repetition time/echo time, 19/10 ms; flip angle, 30°; scan matrix, 256 × 256 pixels; field of view, 256 × 256 mm; number of excitations, 1).

Data analysis

The tissue concentration of radioactivity was obtained from volumes of interest (VOIs) defined on PET images with reference to the individual MRIs co-registered on summated PET images and a brain atlas. The regions were the right and left dorsal caudate, dorsal putamen, ventral caudate, and ventral putamen. Each VOI consisted of three slices. The dorsal boundary of the dorsal caudate was at the level of the interventricular foramen of Monro. The dorsal boundary of the dorsal putamen was two slices lower than that of the dorsal caudate. The ventral boundary of the ventral caudate was at the level of the lower boundary of the third ventricle. The ventral boundary of the ventral putamen was one slice higher than that of the ventral caudate. Quantitative analysis was

Table 1. [^{11}C]raclopride BP_{ND} (mean ± S.D.) in the striatal regions of smokers and non-smokers

	Smokers		Non-smokers	
	Placebo	Nicotine	Placebo	Nicotine
Right dorsal caudate	3.00 ± 0.16	2.87 ± 0.26	2.89 ± 0.48	2.93 ± 0.30
Left dorsal caudate	3.02 ± 0.22	2.85 ± 0.33	2.84 ± 0.36	2.93 ± 0.28
Right dorsal putamen	3.77 ± 0.33	3.52 ± 0.47	3.67 ± 0.39	3.62 ± 0.24
Left dorsal putamen	3.72 ± 0.39	3.50 ± 0.43	3.59 ± 0.42	3.65 ± 0.23
Right ventral caudate	2.74 ± 0.24	2.44 ± 0.18	2.47 ± 0.27	2.55 ± 0.29
Left ventral caudate	2.77 ± 0.26	2.52 ± 0.22	2.56 ± 0.36	2.62 ± 0.25
Right ventral putamen	3.66 ± 0.25	3.31 ± 0.21	3.27 ± 0.39	3.35 ± 0.32
Left ventral putamen	3.53 ± 0.40	3.30 ± 0.25	3.33 ± 0.43	3.41 ± 0.25
Striatal region[a]	3.28 ± 0.32	3.04 ± 0.24	3.08 ± 0.32	3.13 ± 0.24

BP_{ND}, Non-displaceable binding potential.
A three-way repeated-measure ANOVA revealed a significant drug × group interaction.
[a] Post-hoc analysis revealed that overall BP_{ND} values of the striatal region in the nicotine condition were significantly lower than in placebo in smokers. The BP_{ND} value of the striatal region is the mean of pooled data across ROIs. There was no main effect of subject group ($F_{1,10}=0.12$, $p=0.74$).

performed using the simplified reference tissue model (Lammertsma and Hume, 1996). The cerebellum was used as reference region because it has been shown to be almost devoid of dopamine D_2 receptors (Olsson et al., 1999; Suhara et al., 1999). The non-displaceable binding potential (BP_{ND}) (Innis et al., 2007) values were analysed using a three-way repeated-measures ANOVA with subject group (smokers, non-smokers) as a between-subjects factor and drug (nicotine, placebo) and ROI as within-subjects factors. Statistical significance of $p<0.05$ was set for the analysis. To examine the relation between regional [^{11}C]raclopride BP_{ND} and the degree of nicotine dependence, Pearson correlation coefficients between the BP_{ND} of each VOI of both nicotine and placebo conditions and the FTND score were calculated. In addition, in order to explore the relation between nicotine-induced dopamine release and nicotine dependence, correlations between the change in [^{11}C]raclopride BP_{ND} of each VOI and FTND score were calculated. The threshold for significance was set at $p=0.05/8=0.006$ to avoid type 1 errors. To investigate detailed regions, parametric images of BP_{ND} were analysed using SPM (Gunn et al., 1997). Paired t tests were used to compare the BP_{ND} maps following nicotine and placebo administration in both groups. Subtracting the normalized BP_{ND} image in the nicotine condition from that in the placebo condition, we created individual BP_{ND} change maps. Regression analyses were conducted to examine the relation between BP_{ND} change and nicotine dependence.

Results

Nicotine was not detected from any of the participants' plasma samples prior to the PET scans. During the PET scans, the plasma concentrations of nicotine using nicotine gum were 6–16 ng/ml, similar to those achieved by smoking a cigarette. There was no significant difference in the area under the nicotine plasma concentration–time curve (AUC) during PET scans between smokers and non-smokers. BP_{ND} of VOIs in both placebo and nicotine conditions are shown in Table 1. There was a significant drug × subject group interaction ($F_{1,10}=6.42$, $p=0.03$). Post-hoc analysis revealed that BP_{ND} values of the striatal region in the nicotine condition were significantly lower than in placebo in smokers ($F_{1,47}=82.7$, $p<0.001$) but not in non-smokers ($F_{1,47}=1.99$, $p=0.17$). Result of voxel × voxel parametric image analysis indicated significant BP_{ND} differences in the ventral caudate and putamen in smokers (Figure 1a). No significant correlation was found between the BP_{ND} of any VOI and FTND score in either the nicotine or placebo condition. However, the FTND score was correlated with the BP_{ND} difference between the two scanning sessions in the right ventral putamen ($r=0.961$, $p=0.002$). Trend-level correlations were observed between the FTND score and the BP_{ND} difference in the right ventral caudate ($r=0.911$, $p=0.012$) and the left ventral putamen ($r=0.907$, $p=0.012$). These correlations were also confirmed by parametric image analysis (Figure 1b). The BP_{ND} difference in the left ventral putamen

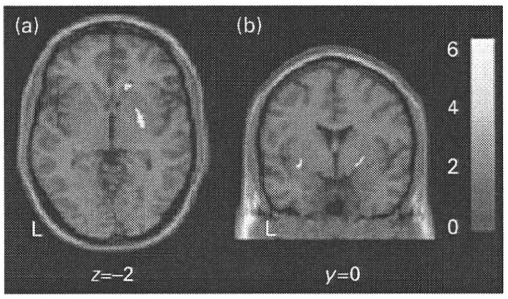

Figure 1. [^{11}C]raclopride non-displaceable binding potential (BP_{ND}) differences between the two scanning sessions in the striatum in smokers, and the correlation with nicotine dependence. (a) Image showing the significant [^{11}C]raclopride BP_{ND} differences in the ventral caudate and putamen in smokers (height threshold at $p<0.005$, uncorrected, and extent threshold of 10 voxels). (b) Image showing the correlation between the BP_{ND} differences in the ventral putamen and the Fagerstrom test for nicotine dependence (FTND) score (height threshold at $p<0.005$, uncorrected, and extent threshold of 10 voxels). The bar shows the range of the t value. Within the images, L indicates left. Numbers in the bottom row indicate the coordinates of the Montreal Neurological Institute brain.

was also correlated with the reduction in craving score ($r=0.940$, $p=0.005$). There was no significant correlation between the BP_{ND} difference and the nicotine plasma concentration represented as AUC.

Discussion

This is the first double-blind, randomized, placebo-controlled study to investigate dopamine release following nicotine administration in both smokers and non-smokers. Smokers showed significant decreases in [^{11}C]raclopride BP_{ND} in the striatum in response to nicotine, and such decrease is thought to reflect the dopamine release following nicotine administration (Brody et al., 2004, 2006). In line with previous studies, there was no significant difference in striatal [^{11}C]raclopride BP_{ND} between smokers and non-smokers in either the nicotine or placebo condition (Scott et al., 2007; Yang et al., 2006). However, only smokers showed significant decreases in [^{11}C]raclopride BP_{ND} in the striatum, while non-smokers showed no detectable changes. The dopamine release in the ventral striatum was correlated with the degree of nicotine dependence and the reduction of craving score in smokers. Enhanced dopamine release in smokers might be a result of the reinforced effect of cigarette smoking. Two human PET studies (Barrett et al., 2004; Montgomery et al., 2007) reported no overall changes in [^{11}C]raclopride binding following nicotine administration in smokers. However, the majority of smokers in the latter study (Montgomery et al., 2007) were of low dependence and the plasma nicotine concentration was lower, whereas the majority of our smokers were moderately or highly dependent. In addition, those studies included female smokers, and gender differences in nicotine effects have been reported (Perkins et al., 1999).

As with other addictive drugs, animal studies have demonstrated that repeated nicotine administration enhances psychomotor responses, rewarding the effects of nicotine and striatal dopamine release in response to nicotine (Benwell and Balfour, 1992). Sensitization of the striatal dopamine response to nicotine has been implicated in the development of nicotine dependence (Benwell and Balfour, 1992).

Nicotinic acetylcholine receptors are expressed on both dopamine neurons and GABA neurons, and axon terminals of glutamatergic input to the midbrain (Laviolette and van der Kooy, 2004) and dopamine neurons in the midbrain are regulated by the balance of excitatory and inhibitory input to the midbrain (Mansvelder and McGehee, 2002). Chronic nicotine exposure was reported to reduce the sensitivity of GABA receptors and result in disinhibition of midbrain dopamine neurons (Amantea and Bowery, 2004). Chronic nicotine administration was also reported to increase the level of ionotropic glutamate receptors in the midbrain and conceivably enhance the excitatory input to the midbrain (Wang et al., 2007). Enhanced striatal dopamine release in smokers might be a consequence of altered control of dopamine release after repeated nicotine exposure.

In conclusion, compared to non-smokers, smokers showed enhanced striatal dopamine release in response to nicotine. The dopamine release in the ventral striatum following nicotine administration was correlated with the degree of nicotine dependence. Although this study is preliminary because of the limited sample, our findings were consistent with the report by Scott et al. (2007) with a similar sample size, suggesting both the feasibility of the nicotine gum method and the importance of the degree of dependence when examining the nicotine effect.

Acknowledgements

This study was supported by a consignment expense for the Molecular Imaging Programme 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 (18790858), and a grant from the Smoking Research Foundation. The authors acknowledge the analytical advice of Takashi Okauchi. We thank Mr Katsuyuki Tanimoto, Mr Takahiro Shiraishi, Mr Akira Ando and Mr Toshio Miyamoto for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Ms Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator.

Statement of Interest

None.

References

Amantea D, Bowery NG (2004). Reduced inhibitory action of a GABAB receptor agonist on [^{3}H]dopamine release from rat ventral tegmental area in vitro after chronic nicotine administration. *BMC Pharmacology 4*, 24.

Barrett SP, Boileau I, Okker J, Pihl RO, Dagher A (2004). The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [^{11}C]raclopride. *Synapse 54*, 65–71.

Benwell ME, Balfour DJ (1992). The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. *British Journal of Pharmacology 105*, 849–856.

Brody AL, Mandelkern MA, Olmstead RE, Scheibal D, Hahn E, Shiraga S, Zamora-Paja E, Farahi J, Saxena S, London ED, McCracken JT (2006). Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Archives of General Psychiatry 63*, 808–816.

Brody AL, Olmstead RE, London ED, Farahi J, Meyer JH, Grossman P, Lee GS, Huang J, Hahn EL, Mandelkern MA (2004). Smoking-induced ventral striatum dopamine release. *American Journal of Psychiatry 161*, 1211–1218.

Dewey SL, Smith GS, Logan J, Brodie JD, Fowler JS, Wolf AP (1993). Striatal binding of the PET ligand ^{11}C-raclopride is altered by drugs that modify synaptic dopamine levels. *Synapse 13*, 350–356.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage 6*, 279–287.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction 86*, 1119–1127.

Innis R, Cunningham VJ, Delforge J, Fujita M, Gunn RN, Holden J, Houle S, Huang S, Ichise M, Ito H, et al. (2007). Consensus nomenclature for in vivo imaging of reversibly-binding radioligands. *Journal of Cerebral Blood Flow and Metabolism*. Published online: 9 May 2007. doi:10.1038/sj.jcbfm.9600493.

Lammertsma AA, Hume SP (1996). Simplified reference tissue model for PET receptor studies. *Neuroimage 4*, 153–158.

Laviolette SR, van der Kooy D (2004). The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. *Nature Reviews Neuroscience 5*, 55–65.

Mansvelder HD, McGehee DS (2002). Cellular and synaptic mechanisms of nicotine addiction. *Journal of Neurobiology 53*, 606–617.

Montgomery AJ, Lingford-Hughes AR, Egerton A, Nutt DJ, Grasby PM (2007). The effect of nicotine on striatal dopamine release in man: a [^{11}C]raclopride PET study. *Synapse 61*, 637–645.

Olausson P, Jentsch JD, Taylor JR (2003). Repeated nicotine exposure enhances reward-related learning in the rat. *Neuropsychopharmacology 28*, 1264–1271.

Olsson H, Halldin C, Swahn CG, Farde L (1999). Quantification of [^{11}C]FLB 457 binding to extrastriatal dopamine receptors in the human brain. *Journal of Cerebral Blood Flow and Metabolism 19*, 1164–1173.

Perkins KA, Donny E, Caggiula AR (1999). Sex differences in nicotine effects and self-administration: review of human and animal evidence. *Nicotine & Tobacco Research 1*, 301–315.

Scott DJ, Domino EF, Heitzeg MM, Koeppe RA, Ni L, Guthrie S, Zubieta JK (2007). Smoking modulation of mu-opioid and dopamine D2 receptor-mediated neurotransmission in humans. *Neuropsychopharmacology 32*, 450–457.

Suhara T, Sudo Y, Okauchi T, Maeda J, Kawabe K, Suzuki K, Okubo Y, Nakashima Y, Ito H, Tanada S, Halldin C, Farde L (1999). Extrastriatal dopamine D2 receptor density and affinity in the human brain measured by 3D PET. *International Journal of Neuropsychopharmacology 2*, 73–82.

Tsukada H, Miyasato K, Kakiuchi T, Nishiyama S, Harada N, Domino EF (2002). Comparative effects of methamphetamine and nicotine on the striatal [^{11}C]raclopride binding in unanesthetized monkeys. *Synapse 45*, 207–212.

Wang F, Chen H, Steketee JD, Sharp BM (2007). Upregulation of ionotropic glutamate receptor subunits within specific mesocorticolimbic regions during chronic nicotine self-administration. *Neuropsychopharmacology 32*, 103–109.

Yang YK, Yao WJ, McEvoy JP, Chu CL, Lee IH, Chen PS, Yeh TL, Chiu NT (2006). Striatal dopamine D2/D3 receptor availability in male smokers. *Psychiatry Research 146*, 87–90.

Yasuno F, Ota M, Ando K, Ando T, Maeda J, Ichimiya T, Takano A, Doronbekov TK, Fujimura Y, Nozaki S, Suhara T (2007). Role of ventral striatal dopamine D_1 receptor in cigarette craving. *Biological Psychiatry 61*, 1252–1259.

Psychiatry and Clinical Neurosciences 2008; 62: 214–219 doi:10.1111/j.1440-1819.2008.01757.x

Regular Article

Enhanced activation in the extrastriate body area by goal-directed actions

Hidehiko Takahashi, MD, PhD,[1,2]* Tomohisa Shibuya, MS,[3] Motoichiro Kato, MD, PhD,[4] Takeshi Sassa, MD, PhD,[2] Michihiko Koeda, MD, PhD,[5] Noriaki Yahata, PhD,[6] Tetsuya Suhara, MD, PhD[1] and Yoshiro Okubo, MD, PhD[5]

[1]*Department of Molecular Neuroimaging, National Institute of Radiological Sciences, Chiba,* [2]*Department of Psychiatry, Asai Hospital, Togane,* [3]*Department of Public Health, School of Medicine, Juntendo University,* [4]*Department of Neuropsychiatry, Keio University School of Medicine and Departments of* [5]*Neuropsychiatry and* [6]*Pharmacology, Nippon Medical School, Tokyo, Japan*

Aim: Neuroimaging studies on biological motion have established the view that the posterior superior temporal sulcus (pSTS) is involved in detecting intention of others. Those studies have consistently reported other regions such as body-selective extrastriate body area (EBA) and motion-sensitive middle temporal, in close proximity to pSTS. Whether EBA responds only to static body parts or has a more extended role as part of a system for inferring intention of others has remained an elusive issue. The aim of the present study was to investigate the role of EBA in processing goal-directed actions.

Methods: Twelve healthy volunteers participated in the present study. Using sports-related motions as visual stimuli, brain activations were examined during observation of goal-directed actions and non-goal-directed actions on functional magnetic resonance imaging.

Results: Compared to non-goal-directed actions, goal-directed actions produced greater activations in EBA along with the mirror neuron system.

Conclusions: EBA might contribute to understanding others' actions by representing the dynamic aspects of human motions.

Key words: extrastriate body area, fMRI, goal-directed actions, mirror neuron system, sports.

NEUROIMAGING STUDIES HAVE established the view that the posterior superior temporal sulcus (pSTS) plays a crucial role in processing biological motion,[1–4] and it has been suggested that the pSTS constitutes a part of the human mirror neuron systems (MNS) through which observed actions of others are internally represented,[5,6] and has a more general function in social cognition such as detecting intention of others[7–9] and behavior of agents.[3] But passive viewing of biological motion has consistently activated other regions of the posterior temporal–occipital cortex including body-selective extrastriate body area (EBA)[10] and motion-sensitive middle temporal (MT),[11] in close proximity to pSTS.[12–14]

Studies about biological motion have used point-light animation of simple action, and scrambled or occluded motion has been used in control condition. Therefore, the use of low-level stimuli as controls would make it difficult to clarify whether EBA and MT are, respectively, involved only in body and motion-sensitive low-level visual processing or lie in a part of a system for inferring the action and intention of others, such as STS. In the present study we compared brain activation in response to more complex meaningful biological motion with that to complex non-meaningful biological motion. We used sports-related motion and sports-unrelated motion for meaningful and non-meaningful biological motion,

Correspondence: Hidehiko Takahashi, MD, PhD, Molecular Imaging Center, Department of Molecular Neuroimaging, National Institute of Radiological Sciences 9-1, 4-chome, Anagawa, Inage-ku, Chiba 263-8555, Japan. Email: hidehiko@nirs.go.jp
Received 1 August 2007; revised 4 September 2007; accepted 19 October 2007.

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

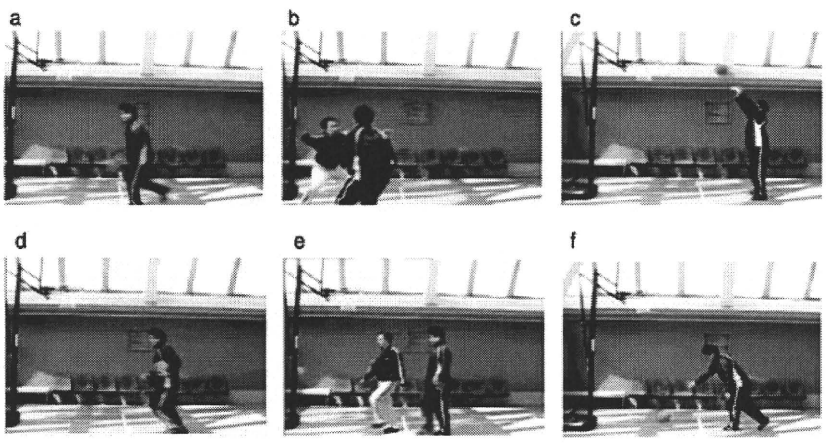

Figure 1. Sample of still frames from (a–c) basketball-related motions and (d–f) basketball-unrelated motions. (a) Dribbling; (b) man-to-man; (c) shooting; (d) carrying; (e) crossing; (f) rolling.

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

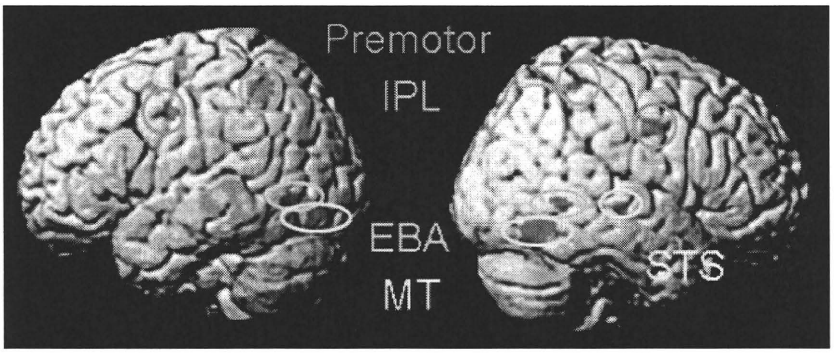

Figure 2. Brain activations in response to sports-related motion minus sports-unrelated motion. Significant activations in extrastriate body area (EBA), middle temporal (MT), superior temporal sulcus (STS), inferior parietal lobule (IPL) and premotor areas are shown. Within the images, L indicates left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

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.

REFERENCES

[1] Akiyama T, Kato M, Muramatsu T, Saito F, Nakachi R, Kashima H. A deficit in discriminating gaze direction in a case with right superior temporal gyrus lesion. *Neuropsychologia* 2006; **44**: 161–170.

[2] Allison T, Puce A, McCarthy G. Social perception from visual cues: Role of the STS region. *Trends Cogn. Sci.* 2000; **4**: 267–278.

[3] Frith U, Frith CD. Development and neurophysiology of mentalizing. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 2003; **358**: 459–473.

[4] Puce A, Perrett D. Electrophysiology and brain imaging of biological motion. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 2003; **358**: 435–445.

[5] Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. *Nat. Rev. Neurosci.* 2006; **7**: 942–951.

[6] Rizzolatti G, Craighero L. The mirror-neuron system. *Annu. Rev. Neurosci.* 2004; **27**: 169–192.

[7] Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. *Trends Cogn. Sci.* 2003; **7**: 77–83.

[8] Takahashi H, Yahata N, Koeda M, Matsuda T, Asai K, Okubo Y. Brain activation associated with evaluative processes of guilt and embarrassment: An fMRI study. *Neuroimage* 2004; **23**: 967–974.

[9] Takahashi H, Matsuura M, Koeda M *et al.* Brain activations during judgments of positive self-conscious emotion and positive basic emotion: Pride and joy. *Cereb. Cortex* 2007 Epub ahead of print.

[10] Downing PE, Jiang Y, Shuman M, Kanwisher N. A cortical area selective for visual processing of the human body. *Science* 2001; **293**: 2470–2473.

[11] Tootell RB, Reppas JB, Kwong KK *et al.* Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J. Neurosci.* 1995; **15**: 3215–3230.

[12] Blake R, Shiffrar M. Perception of human motion. *Annu. Rev. Psychol.* 2007; **58**: 47–73.

[13] Hirai M, Fukushima H, Hiraki K. An event-related potentials study of biological motion perception in humans. *Neurosci. Lett.* 2003; **344**: 41–44.

[14] Peelen MV, Wiggett AJ, Downing PE. Patterns of fMRI activity dissociate overlapping functional brain areas that respond to biological motion. *Neuron* 2006; **49**: 815–822.

[15] Peelen MV, Downing PE. Is the extrastriate body area involved in motor actions? *Nat. Neurosci.* 2005; **8** (125): 125–126.

[16] Astafiev SV, Stanley CM, Shulman GL, Corbetta M. Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nat. Neurosci.* 2004; **7**: 542–548.

[17] Jackson PL, Meltzoff AN, Decety J. Neural circuits involved in imitation and perspective-taking. *Neuroimage* 2006; **31**: 429–439.

[18] Jeannerod M. Visual and action cues contribute to the self-other distinction. *Nat. Neurosci.* 2004; **7**: 422–423.

[19] Pelphrey KA, Mitchell TV, McKeown MJ, Goldstein J, Allison T, McCarthy G. Brain activity evoked by the perception of human walking: Controlling for meaningful coherent motion. *J. Neurosci.* 2003; **23**: 6819–6825.

[20] Grezes J, Decety J. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: A meta-analysis. *Hum. Brain Mapp.* 2001; **12**: 1–19.

[21] Brass M, Heyes C. Imitation: Is cognitive neuroscience solving the correspondence problem? *Trends Cogn. Sci.* 2005; **9**: 489–495.

[22] Flanagan JR, Johansson RS. Action plans used in action observation. *Nature* 2003; **424**: 769–771.

[23] Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G. Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol.* 2005; **3**: e79.

[24] Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: From action organization to intention understanding. *Science* 2005; **308**: 662–667.

[25] Michels L, Lappe M, Vaina LM. Visual areas involved in the perception of human movement from dynamic form analysis. *Neuroreport* 2005; **16**: 1037–1041.

[26] Peuskens H, Vanrie J, Verfaillie K, Orban GA. Specificity of regions processing biological motion. *Eur. J. Neurosci.* 2005; **21**: 2864–2875.

[27] Downing PE, Peelen MV, Wiggett AJ, Tew BD. The role of the extrastriate body area in action perception. *Soc. Neurosci.* 2006; **1**: 52–62.

[28] Cheng Y, Meltzoff AN, Decety J. Motivation modulates the activity of the human mirror-neuron system. *Cereb. Cortex* 2006; **17**: 1979–1986.
[29] Kourtzi Z, Kanwisher N. Activation in human MT/MST by static images with implied motion. *J. Cogn. Neurosci.* 2000; **12**: 48–55.
[30] Downing PE, Wiggett AJ, Peelen MV. Functional magnetic resonance imaging investigation of overlapping lateral occipitotemporal activations using multi-voxel pattern analysis. *J. Neurosci.* 2007; **27**: 226–233.
[31] Spiridon M, Fischl B, Kanwisher N. Location and spatial profile of category-specific regions in human extrastriate cortex. *Hum. Brain Mapp.* 2006; **27**: 77–89.
[32] Miki K, Watanabe S, Honda Y, Nakamura M, Kakigi R. Effects of face contour and features on early occipitotemporal activity when viewing eye movement. *Neuroimage* 2007; **35**: 1624–1635.

International Journal of Mental Health Systems

BioMed Central

Research

Open Access

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

Published: 26 September 2008

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

Received: 23 August 2008
Accepted: 26 September 2008

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

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

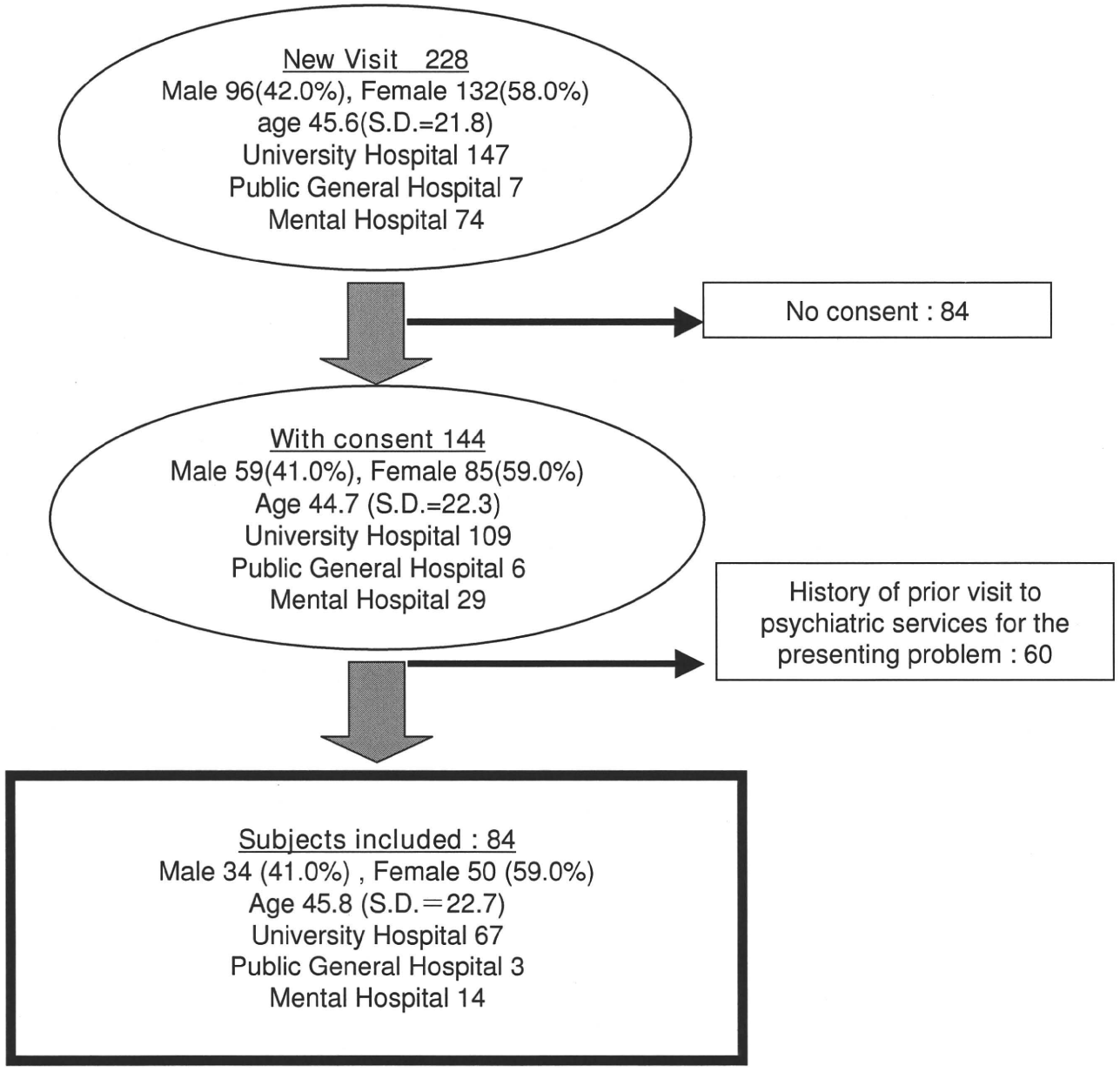

Figure 1
Inclusion procedure and demographics of the subjects. Figure legend text.

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

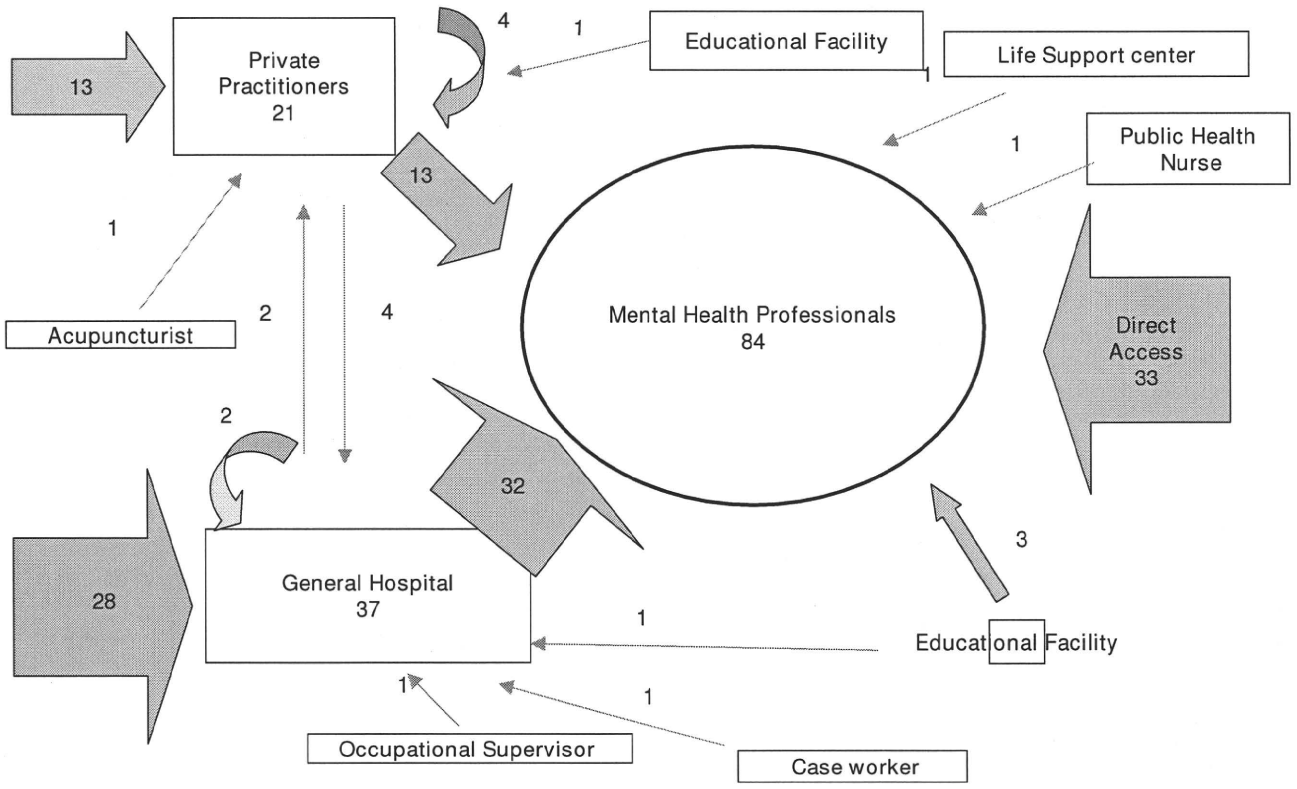

Figure 2
The Pathway Diagram. Figures indicate numbers of subjects who took each pathway or consulted each carer. Curved arrows indicate recursive pathways, where patients have gone from one to another of the same type of carer.

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.

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.

References

1. Goldberg DP, Huxley P: *Mental Illness in the Community: The Pathway to Psychiatric Care* London: Tavistock Press; 1980.
2. Gater R, de Almeida e Sousa B, Barrientos G, Caraveo J, Chandrashekar CR, Dhadphale M, Goldberg D, al Kathiri AH, Mubbashar M, Silhan K, *et al.*: **The pathways to psychiatric care: a cross-cultural study.** *Psychol Med* 1991, **21**:761-74.
3. Gater R, Jordanova V, Maric N, Alikaj V, Bajs M, Cavic T, Dimitrov H, Iosub D, Mihai A, Szalontay AS, Helmchen H, Sartorius N: **Pathways to psychiatric care in Eastern Europe.** *Br J Psychiatry* 2005, **186**:529-35.
4. Gater R, Goldberg D: **Pathways to psychiatric care in South Manchester.** *Br J Psychiatry* 1991, **159**:90-6.
5. Balestrieri M, Bon MG, Rodriguez-Sacristan A, Tansella M: **Pathways to psychiatric care in south-Verona, Italy.** *Psychol Med* 1994, **24**:641-9.
6. Kurihara T, Kato M, Reverger R, Tirta IG: **Pathway to psychiatric care in Bali.** *Psychiatry Clin Neurosci* 2006, **60**:204-10.
7. Abiodun OA: **Pathways to mental health care in Nigeria.** *Psychiatr Serv* 1995, **46**:823-6.
8. Kiliç C, Rezaki M, Ustün TB, Gater RA: **Pathways to psychiatric care in Ankara.** *Soc Psychiatry Psychiatr Epidemiol* 1994, **29**:131-6.
9. Pawłowski T, Kiejna A: **Pathways to psychiatric care and reform of the public health care system in Poland.** *Eur Psychiatry* 2004, **19**:168-71.
10. Steel Z, McDonald R, Silove D, Bauman A, Sandford P, Herron J, Minas IH: **Pathways to the first contact with specialist mental health care.** *Aust N Z J Psychiatry* 2006, **40**:347-54.