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

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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

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

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

5. Conclusion

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

Role of funding source

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

Contributors

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

Conflict of interest

All the authors have no conflict of interest.

Acknowledgement

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

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders DSM-IV. American Psychiatric Association, Washington, DC, USA.

Andreasen, N.C., O'Leary, D.S., Flaum, M., Nopoulos, P., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D., 1997. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 349, 1730–1734.

Braff, D.L., Swerdlow, N.R., Geyer, M.A., 1999. Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. Am. J. Psychiatry 156, 596–602.

Breier, A., Su, T.P., Saunders, R., Carson, R.E., Kolachana, B.S., de Bartolomeis, A., Weinberger, D.R., Weisenfeld, N., Malhotra, A.K., Eckelman, W.C., Pickar, D., 1997. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc. Natl. Acad. Sci. U. S. A. 94, 2569–2574.

Buchsbaum, M.S., Someya, T., Teng, C.Y., Abel, L., Chin, S., Najafi, A., Haier, R.J., Wu, J., Bunney Jr., W.E., 1996. PET and MRI of the thalamus in never-medicated patients with schizophrenia. Am. J. Psychiatry 153, 191–199.

Buchsbaum, M.S., Christian, B.T., Lehrer, D.S., Narayanan, T.K., Shi, B., Mantil, J., Kemether, E., Oakes, T.R., Mukherjee, J., 2006. D_2/ D_3 dopamine receptor binding with [^{18}F]fallypride in thalamus and cortex of patients with schizophrenia. Schizophr. Res. 85, 232–244.

Carlsson, A., Waters, N., Waters, S., Carlsson, M.L., 2000. Network interactions in schizophrenia — therapeutic implications. Brain Res. Brain Res. Rev. 31, 342–349.

Clark, C., Kopala, L., Li, D.K., Hurwitz, T., 2001. Regional cerebral glucose metabolism in never-medicated patients with schizophrenia. Can. J. Psychiatry 46, 340–345.

Clinton, S.M., Meador-Woodruff, J.H., 2004. Thalamic dysfunction in schizophrenia: neurochemical, neuropathological, and in vivo imaging abnormalities. Schizophr. Res. 69, 237–253.

Dao-Castellana, M.H., Paillere-Martinot, M.L., Hantraye, P., Attar-Levy, D., Remy, P., Crouzel, C., Artiges, E., Feline, A., Syrota, A., Martinot, J.L., 1997. Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophr. Res. 23, 167–174.

Dhawan, V., Ishikawa, T., Patlak, C., Chaly, T., Robeson, W., Belakhlef, A., Margouleff, C., Mandel, F., Eidelberg, D., 1996. Combined FDOPA and 3OMFD PET studies in Parkinson's disease. J. Nucl. Med. 37, 209–216.

Elkashef, A.M., Doudet, D., Bryant, T., Cohen, R.M., Li, S.H., Wyatt, R.J., 2000. 6-(18)F-DOPA PET study in patients with schizophrenia. Positron emission tomography. Psychiatry Res. 100, 1–11.

Farde, L., Wiesel, F.A., Stone-Elander, S., Halldin, C., Nordström, A.L., Hall, H., Sedvall, G., 1990. D_2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [^{11}C] raclopride. Arch. Gen. Psychiatry 47, 213–219.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders: SCID-1 Clinician Version. American Psychiatric Publishing, Inc., Arlington, USA.

Gefvert, O., Lindström, L.H., Waters, N., Waters, S., Carlsson, A., Tedroff, J., 2003. Different corticostriatal patterns of L-DOPA utilization in patients with untreated schizophrenia and patients treated with classical antipsychotics or clozapine. Scand. J. Psychol. 44, 289–292.

Gjedde, A., 1982. Calculation of cerebral glucose phosphorylation from brain uptake of glucose analogs in vivo: a re-examination. Brain Res. 257, 237–274.

Gründer, G., Vernaleken, I., Muller, M.J., Davids, E., Heydari, N., Buchholz, H.G., Bartenstein, P., Munk, O.L., Stoeter, P., Wong, D.F., Gjedde, A., Cumming, P., 2003. Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients in vivo. Neuropsychopharmacology 28, 787–794.

Hazlett, E.A., Buchsbaum, M.S., Byne, W., Wei, T.C., Spiegel-Cohen, J., Geneve, C., Kinderlehrer, R., Haznedar, M.M., Shihabuddin, L., Siever, L.J., 1999. Three-dimensional analysis with MRI and PET of the size, shape, and function of the thalamus in the schizophrenia spectrum. Am. J. Psychiatry 156, 1190–1199.

Hazlett, E.A., Buchsbaum, M.S., Kemether, E., Bloom, R., Platholi, J., Brickman, A.M., Shihabuddin, L., Tang, C., Byne, W., 2004. Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia. Am. J. Psychiatry 161, 305–314.

Hietala, J., Syvalahti, E., Vuorio, K., Rakkolainen, V., Bergman, J., Haaparanta, M., Solin, O., Kuoppamaki, M., Kirvela, O., Ruotsalainen, U., Salokangas, R., 1995. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346, 1130–1131.

Hietala, J., Syvalahti, E., Vilkman, H., Vuorio, K., Rakkolainen, V., Bergman, J., Haaparanta, M., Solin, O., Kuoppamaki, M., Eronen, E., Ruotsalainen, U., Salokangas, R.K., 1999. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. Schizophr. Res. 35, 41–50.

Igarashi, Y., Hayashi, N., Yamashina, M., Otsuka, N., Kuroki, N., Anzai, N., Kazamatsuri, H., 1998. Interrater reliability of the Japanese version of the positive and negative syndrome scale and the appraisal of its training effect. Psychiatry Clin. Neurosci. 52, 467–470.

Ito, H., Ota, M., Ikoma, Y., Seki, C., Yasuno, F., Takano, A., Maeda, J., Nakao, R., Suzuki, K., Suhara, T., 2006. Quantitative analysis of dopamine synthesis in human brain using positron emission tomography with L-[beta-^{11}C] DOPA. Nucl. Med. Commun. 27, 723–731.

Kim, J.J., Mohamed, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D., 2000. Regional neural dysfunctions in chronic schizophrenia studied with positron emission tomography. Am. J. Psychiatry 157, 542–548.

Kircher, T.T., Liddle, P.F., Brammer, M.J., Williams, S.C., Murray, R.M., McGuire, P.K., 2002. Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia. Psychol. Med. 32, 439–449.

Kumakura, Y., Cumming, P., Vernaleken, I., Buchholz, H.G., Siessmeier, T., Heinz, A., Kienast, T., Bartenstein, P., Gründer, G., 2007. Elevated [^{18}F] fluorodopamine turnover in brain of patients with schizophrenia: an [^{18}F]fluorodopa/positron emission tomography study. J. Neurosci. 27, 8080–8087.

Laakso, A., Vilkman, H., Alakare, B., Haaparanta, M., Bergman, J., Solin, O., Peurasaari, J., Rakkolainen, V., Syvalahti, E., Hietala, J., 2000. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. Am. J. Psychiatry 157, 269–271.

Laakso, A., Vilkman, H., Bergman, J., Haaparanta, M., Solin, O., Syvalahti, E., Salokangas, R.K., Hietala, J., 2002. Sex differences in striatal presynaptic dopamine synthesis capacity in healthy subjects. Biol. Psychiatry 52, 759–763.

Laruelle, M., Abi-Dargham, A., van Dyck, C.H., Gil, R., D'Souza, C.D., Erdos, J., McCance, E., Rosenblatt, W., Fingado, C., Zoghbi, S.S., Baldwin, R.M., Seibyl, J.P., Krystal, J.H., Charney, D.S., Innis, R.B., 1996. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc. Natl. Acad. Sci. U. S. A. 93, 9235–9240.

Laruelle, M., Abi-Dargham, A., van Dyck, C., Gil, R., D'Souza, D.C., Krystal, J., Seibyl, J., Baldwin, R., Innis, R., 2000. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [^{123}I]beta-CIT. Biol. Psychiatry 47, 371–379.

Lindström, L.H., Gefvert, O., Hagberg, G., Lundberg, T., Bergstrom, M., Hartvig, P., Langström, B., 1999. Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-^{11}C) DOPA and PET. Biol. Psychiatry 46, 681–688.

Mai, J., Assheuer, J., Paxinos, G., 1997. Atlas of the Human Brain. Academic Press, New York.

McGowan, S., Lawrence, A.D., Sales, T., Quested, D., Grasby, P., 2004. Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [^{18}F]fluorodopa study. Arch. Gen. Psychiatry 61, 134–142.

McGraw, K.O., Wong, S.P., 1996. Forming inferences about some intraclass correlation coefficients. Psychol. Methods 1, 30–46.

Melega, W.P., Luxen, A., Perlmutter, M.M., Nissenson, C.H., Phelps, M.E., Barrio, J.R., 1990. Comparative in vivo metabolism of 6-[^{18}F]fluoro-L-dopa and [^{3}H]L-dopa in rats. Biochem. Pharmacol. 39, 1853–1860.

Mitelman, S.A., Byne, W., Kemether, E.M., Hazlett, E.A., Buchsbaum, M.S., 2005. Metabolic disconnection between the mediodorsal nucleus of the thalamus and cortical Brodmann's areas of the left hemisphere in schizophrenia. Am. J. Psychiatry 162, 1733–1735.

Nordström, A.L., Farde, L., Eriksson, L., Halldin, C., 1995. No elevated D_2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [^{11}C]N-methylspiperone. Psychiatry Res. 61, 67–83.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9, 97–113.

Ota, M., Yasuno, F., Ito, H., Seki, C., Nozaki, S., Asada, T., Suhara, T., 2006. Age-related decline of dopamine synthesis in the living human brain measured by positron emission tomography with L-[beta-^{11}C]DOPA. Life Sci. 79, 730–736.

Parent, A., 1990. Extrinsic connections of the basal ganglia. Trends Neurosci. 13, 254–258.

Patlak, C.S., Blasberg, R.G., 1985. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J. Cereb. Blood Flow Metab. 5, 584–590.

Reith, J., Benkelfat, C., Sherwin, A., Yasuhara, Y., Kuwabara, H., Andermann, F., Bachneff, S., Cumming, P., Diksic, M., Dyve, S.E., Etienne, P., Evans, A.C., Lal, S., Shevell, M., Savard, G., Wong, D.F., Chouinard, G., Gjedde, A., 1994. Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc. Natl. Acad. Sci. U. S. A. 91, 11651–11654.

Resnick, S.M., Gur, R.E., Alavi, A., Gur, R.C., Reivich, M., 1988. Positron emission tomography and subcortical glucose metabolism in schizophrenia. Psychiatry Res. 24, 1–11.

Salem, J.E., Kring, A.M., 1998. The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. Clin. Psychol. Rev. 18, 795–819.

Salokangas, R.K., Vilkman, H., Ilonen, T., Taiminen, T., Bergman, J., Haaparanta, M., Solin, O., Alanen, A., Syvalahti, E., Hietala, J., 2000. High levels of dopamine activity in the basal ganglia of cigarette smokers. Am. J. Psychiatry 157, 632–634.

Schmitt, G.J., Meisenzahl, E.M., Frodl, T., La Fougere, C., Hahn, K., Moller, H.J., Dresel, S., 2005. The striatal dopamine transporter in first-episode, drug-naive schizophrenic patients: evaluation by the new SPECT-ligand [^{99m}Tc] TRODAT-1. J. Psychopharmacol. 19, 488–493.

Shergill, S.S., Brammer, M.J., Williams, S.C., Murray, R.M., McGuire, P.K., 2000. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch. Gen. Psychiatry 57, 1033–1038.

Suhara, T., Okubo, Y., Yasuno, F., Sudo, Y., Inoue, M., Ichimiya, T., Nakashima, Y., Nakayama, K., Tanada, S., Suzuki, K., Halldin, C., Farde, L., 2002. Decreased dopamine D_2 receptor binding in the anterior cingulate cortex in schizophrenia. Arch. Gen. Psychiatry 59, 25–30.

Takahashi, H., Higuchi, M., Suhara, T., 2006. The role of extrastriatal dopamine D_2 receptors in schizophrenia. Biol. Psychiatry 59, 919–928.

Talvik, M., Nordström, A.L., Olsson, H., Halldin, C., Farde, L., 2003. Decreased thalamic D_2/ D_3 receptor binding in drug-naive patients with schizophrenia: a PET study with [^{11}C]FLB 457. Int. J. Neuropsychopharmacol. 6, 361–370.

Talvik, M., Nordström, A.L., Okubo, Y., Olsson, H., Borg, J., Halldin, C., Farde, L., 2006. Dopamine D_2 receptor binding in drug-naive patients with schizophrenia examined with raclopride-C11 and positron emission tomography. Psychiatry Res. 148, 165–173.

Torstenson, R., Tedroff, J., Hartvig, P., Fasth, K.J., Langstrom, B., 1999. A comparison of ^{11}C-labeled L-DOPA and L-fluorodopa as positron emission tomography tracers for the presynaptic dopaminergic system. J. Cereb. Blood Flow Metab. 19, 1142–1149.

Tuppurainen, H., Kuikka, J., Viinamaki, H., Husso-Saastamoinen, M., Bergstrom, K., Tiihonen, J., 2003. Extrastriatal dopamine D_2/ D_3 receptor density and distribution in drug-naïve schizophrenic patients. Mol. Psychiatry 8, 453–455.

Wahl, L., Chirakal, R., Firnau, G., Garnett, E.S., Nahmias, C., 1994. The distribution and kinetics of [^{18}F]6-fluoro-3-O-methyl-L-dopa in the human brain. J. Cereb. Blood Flow Metab. 14, 664–670.

Wong, D.F., Wagner Jr., H.N., Tune, L.E., Dannals, R.F., Pearlson, G.D., Links, J.M., Tamminga, C.A., Broussolle, E.P., Ravert, H.T., Wilson, A.A., Toung, J.K., Malat, J., Williams, J.A., O'Tuama, L.A., Snyder, S.H., Kuhar, M.J., Gjedde, A., 1986. Positron emission tomography reveals elevated D_2 dopamine receptors in drug-naïve schizophrenics. Science 234, 1558–1563.

Woodruff, P.W., Wright, I.C., Bullmore, E.T., Brammer, M., Howard, R.J., Williams, S.C., Shapleske, J., Rossell, S., David, A.S., McGuire, P.K., Murray, R.M., 1997. Auditory hallucinations and the temporal cortical response to speech in schizophrenia: a functional magnetic resonance imaging study. Am. J. Psychiatry 154, 1676–1682.

Yang, Y.K., Yu, L., Yeh, T.L., Chiu, N.T., Chen, P.S., Lee, I.H., 2004. Associated alterations of striatal dopamine D_2/ D_3 receptor and transporter binding in drug-naive patients with schizophrenia: a dual-isotope SPECT study. Am. J. Psychiatry 161, 1496–1498.

Yasuno, F., Suhara, T., Okubo, Y., Sudo, Y., Inoue, M., Ichimiya, T., Takano, A., Nakayama, K., Halldin, C., Farde, L., 2004. Low dopamine D_2 receptor binding in subregions of the thalamus in schizophrenia. Am. J. Psychiatry 161, 1016–1022.

Young, K.A., Randall, P.K., Wilcox, R.E., 1995. Startle and sensorimotor correlates of ventral thalamic dopamine and GABA in rodents. Neuroreport 6, 2495–2499.

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

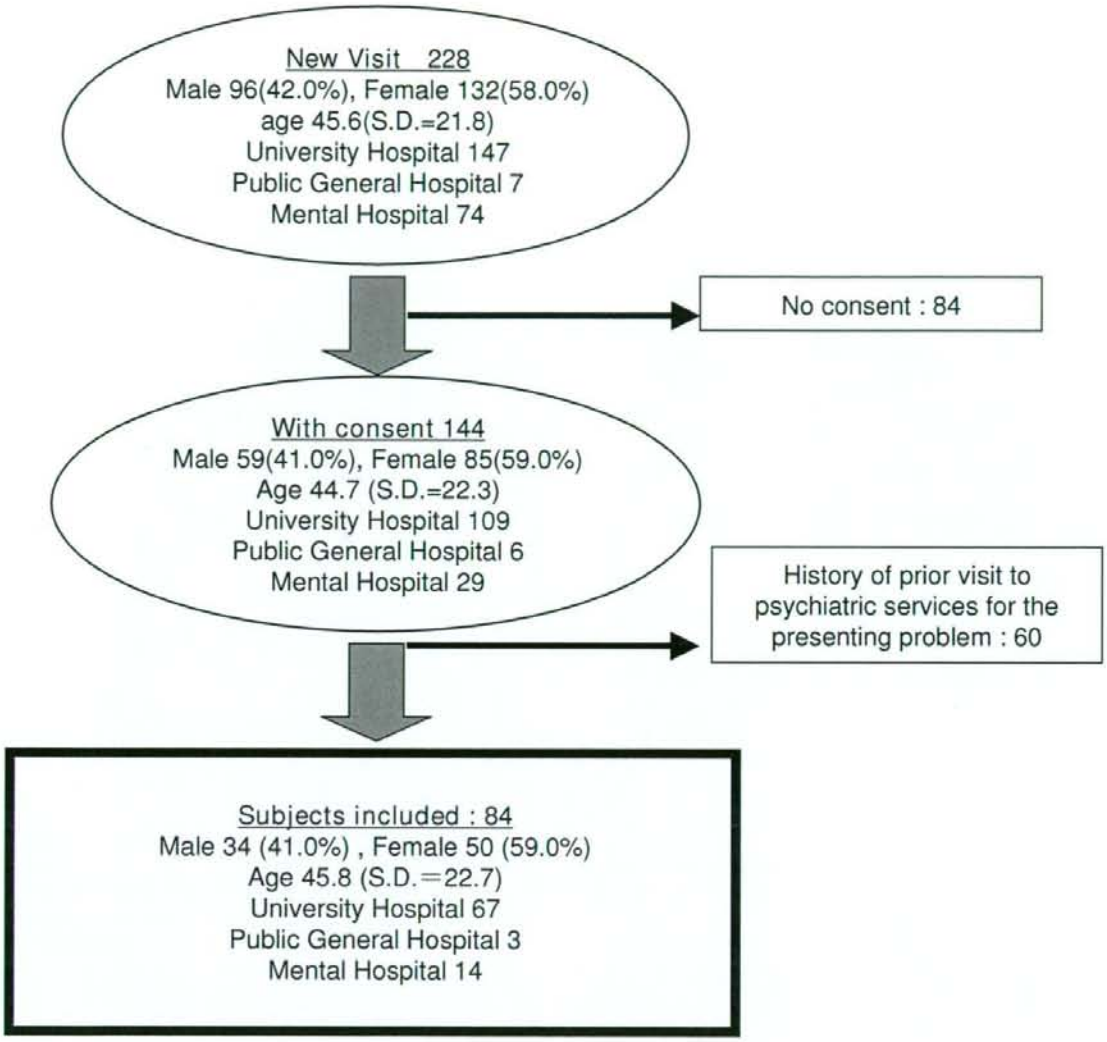

Figure 1
Inclusion procedure and demographics of the subjects. Figure legend text.

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

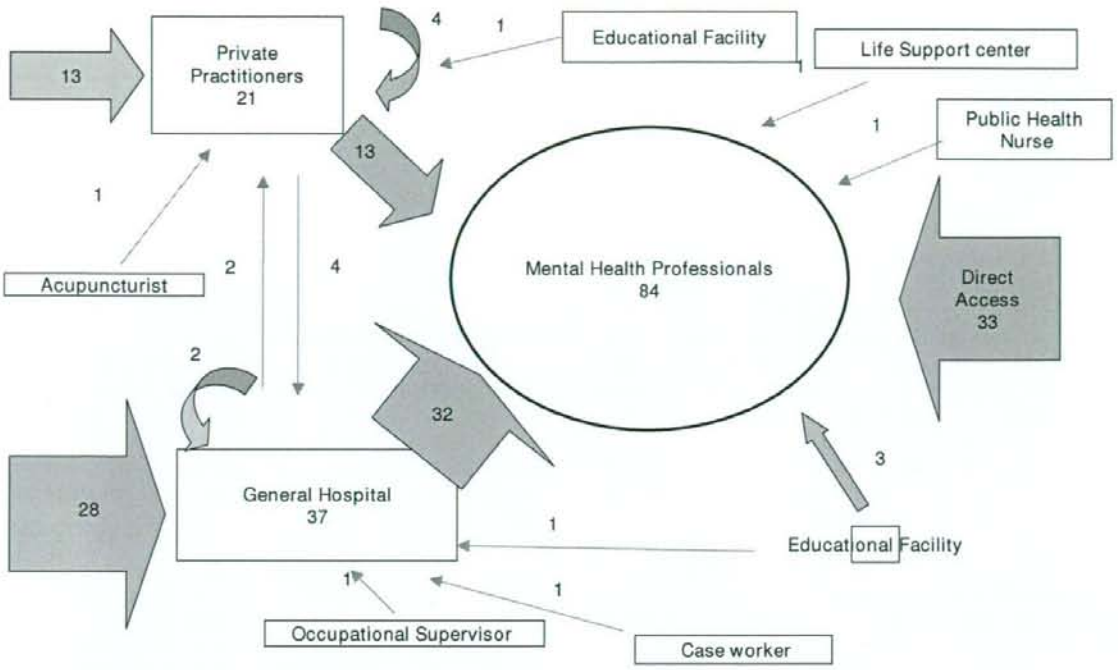

Figure 2
The Pathway Diagram. Figures indicate numbers of subjects who took each pathway or consulted each carer. Curved arrows indicate recursive pathways, where patients have gone from one to another of the same type of carer.

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.

Quantitative Analysis of NK_1 Receptor in the Human Brain Using PET with ^{18}F-FE-SPA-RQ

Masaki Okumura[1,2], Ryosuke Arakawa[1,2], Hiroshi Ito[1], Chie Seki[1], Hidehiko Takahashi[1], Harumasa Takano[1], Eisuke Haneda[1,3], Ryuji Nakao[4], Hidenori Suzuki[3], Kazutoshi Suzuki[4], Yoshiro Okubo[2], and Tetsuya Suhara[1]

[1]Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan; [2]Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan; [3]Department of Pharmacology, Nippon Medical School, Tokyo, Japan; and [4]Molecular Probe Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan

^{18}F-fluoroethyl-SPA-RQ (^{18}F-FE-SPA-RQ) was recently developed as a radioligand for the measurement of neurokinin 1 (NK_1) receptor with PET. In this study, we used ^{18}F-FE-SPA-RQ with PET to visualize and quantify NK_1 receptor in the human brain. **Methods:** PET scans were performed on 7 healthy men after intravenous injection of ^{18}F-FE-SPA-RQ. Binding potential (BP_{ND}) was calculated by the indirect kinetic, simplified reference tissue model (SRTM), and ratio methods. The indirect kinetic method was used as the gold standard method and was compared with the SRTM method, with scan times of 180, 270, and 330 min, and with the ratio method, with time integration intervals of 120–180, 210–270, and 300–330 min. The cerebellum was used as the reference brain region. **Results:** Regional radioactivity was highest in the caudate head and putamen; mid level in the parahippocampus, cerebral cortex, and thalamus; and lowest in the cerebellum. BP_{ND} values by the indirect kinetic method were 3.15 ± 0.36, 3.11 ± 0.66, 1.17 ± 0.25, and 0.46 ± 0.14 in the caudate, putamen, parahippocampal region, and thalamus, respectively. For cerebral cortical regions, BP_{ND} values by the indirect kinetic method were 0.94 ± 0.23, 0.82 ± 0.15, 0.76 ± 0.15, and 0.69 ± 0.16 in the occipital, temporal, frontal, and anterior cingulate cortices, respectively. BP_{ND} values by the SRTM and ratio methods were in good agreement with those by the indirect kinetic method (r = 0.94–0.98). **Conclusion:** The regional distribution of ^{18}F-FE-SPA-RQ was in agreement with previous PET studies and postmortem studies of NK_1 receptor in the human brain. The ratio method will be useful for clinical research of psychiatric disorders, for the estimation of NK_1 receptor without arterial blood sampling and long dynamic PET.

Key Words: NK_1 receptor; substance P; ^{18}F-FE-SPA-RQ; PET; human brain

J Nucl Med 2008; 49:1749–1755
DOI: 10.2967/jnumed.108.054353

Tachykinins are a family of neuropeptides that serve as neurotransmitters in the central nervous system (CNS) and peripheral nervous system (PNS). Three major mammalian tachykinins—substance P (SP), neurokinin A, and neurokinin B—are known, and they share a consensus amino acid sequence (-Phe-X-Gly-Leu-Met-NH_2) in their carboxyl terminals (*1–4*). SP is a well-characterized neuropeptide, participating in neurotransmission by itself or synergistically with other neurotransmitters such as monoamines, acetylcholine, and glutamate in nerve terminals. Receptors for tachykinins—termed neurokinin 1 (NK_1), NK_2, and NK_3 receptors—have been identified (all are G protein–coupled 7-transmembrane receptors) and demonstrated to selectively show high affinity for SP, neurokinin A, and neurokinin B, respectively (*5,6*). NK_1 receptors are expressed in both CNS and PNS, whereas NK_2 and NK_3 receptors are expressed in PNS and CNS, respectively (*7,8*). SP and NK_1 receptors have been shown to play significant roles in pain (*9*), emesis (*10*), neuroinflammation (*11,12*), vasomotor control, and many gastrointestinal functions. Because the SP–NK_1 system is localized in brain regions (such as the striatum, amygdala, hypothalamus, raphe nucleus, and periaqueductal gray matter) that are involved in the regulation of affective behavior (*7,8*), the activity of the central tachykinergic pathway mediated by SP and NK_1 receptors is conceived to be mechanistically related to psychiatric conditions such as depression and anxiety disorder. Recent clinical trials of the NK_1 receptor antagonist aprepitant have shown that the blockade of SP is a highly effective strategy for the prevention of chemotherapy-induced nausea and vomiting (*13–15*). Aprepitant was recently registered worldwide, and it represents an improvement for antiemetic control during chemotherapy. Early clinical studies also suggested that aprepitant may have antidepressant activity, implicating SP in the modulation of mood and anxiety in humans (*16,17*). However, recent results from phase III clinical trials indicate that aprepitant is not effective for the treatment of depression (*18*).

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

Received May 14, 2008; revision accepted Jul. 14, 2008.
For correspondence or reprints contact: Hiroshi Ito, Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences 4-9-1, Anagawa, Inage-ku, Chiba, 263-8555, Japan.
E-mail: hito@nirs.go.jp

to bind to NK_1 receptors with high affinity and selectivity and applied to in vivo imaging of human brains (*20–22*).

^{18}F-fluoroethyl-SPA-RQ (^{18}F-FE-SPA-RQ) was recently developed as a radioligand for the measurement of NK_1 receptors (*23*). It is the fluoroethyl analog of ^{18}F-SPA-RQ and was designed for brain imaging with reduced radioactive accumulation in bone by slowing the rate of defluorination. ^{18}F-FE-SPA-RQ has higher affinity for NK_1 receptors than does ^{18}F-SPA-RQ (human NK_1 inhibitory concentration of 50% [IC_{50}] = 17 and 67 pM for ^{18}F-FE-SPA-RQ and ^{18}F-SPA-RQ, respectively), and a small-animal PET study has been performed using ^{18}F-FE-SPA-RQ (*24*). In the present study, we aimed to quantify NK_1 receptor binding in the human brain using ^{18}F-FE-SPA-RQ with arterial blood sampling and also to validate noninvasive methods for the quantification without arterial blood sampling.

MATERIALS AND METHODS

Subjects

A total of 7 healthy male subjects (age range, 20–31 y; mean ± SD, 24.6 ± 4.0 y) participated in this study. All subjects were free of any somatic, neurologic, or psychiatric disorders, and they had no history of current or previous drug abuse. After we described the study to the participants, written informed consent was obtained. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiologic Sciences, Chiba, Japan.

Radioligand

The NK_1 receptor antagonist SPA-RQ (molecular weight, 450M) was labeled with the positron emitter ^{18}F (half-life, 109.8 min). Details of the precursor compound, radiosynthesis, and quality control were described previously (*23,25*). Briefly, ^{18}F-FCH_2CH_2Br was prepared from $^{18}F^-$ and 2-bromoethyl triflate and purified by distillation. ^{18}F-fluoroalkylation of the deprotonated phenolic hydroxyl group in the precursor with FCH_2CH_2Br in dimethyl formamide was performed at 120°C for 10 min. The resultant ^{18}F-FE-SPA-RQ was purified by preparative high-performance liquid chromatography (HPLC). The final product was formulated in saline solution (10 mL) containing polysorbate 80 (75 μL).

PET Procedure

A PET scanner system (ECAT EXACT HR+; CTI-Siemens) was used for all subjects, and a head restraint was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source, and a dynamic PET scan was performed after a 1-min intravenous slow-bolus injection of 210.2–228.8 MBq (221.6 ± 6.7 MBq) of ^{18}F-FE-SPA-RQ. Specific radioactivity of ^{18}F-FE-SPA-RQ was 281.8–487.7 GBq/μmol (355.6 ± 68.7 GBq/μmol). Brain radioactivity was measured from 0 to 90 min (1 min × 10, 2 min × 15, 5 min × 10), from 120 to 180 min (5 min × 12), from 210 to 270 min (5 min × 12), and from 300 to 330 min (5 min × 6). MR images of the brain were acquired with a 1.5-T MRI scanner (Gyroscan NT; Philips). T1-weighted images were obtained at 1-mm slices.

Arterial Blood Sampling and Metabolite Analysis

To obtain the arterial input function, arterial blood samples were taken manually 49 times during PET. Each of the blood samples was centrifuged to obtain plasma and blood cell fractions, and the concentrations of radioactivity in whole blood and in plasma were measured.

The percentage of unchanged ^{18}F-FE-SPA-RQ in plasma was determined by HPLC in 29 of the total blood samples. Acetonitrile was added to each plasma sample, and samples were centrifuged. The supernatant was subjected to radio-HPLC analysis using an XBridge Prep C18 column (Waters) (mobile phase, 6:4 90% acetonitrile:50 mM phosphoric acid). The plasma input function was defined as the radioactivity of plasma multiplied by the percentage of unchanged radioligand. Plasma protein binding was not determined in the present study.

Regions of Interest

All MR images were coregistered to the PET images using a statistical parametric mapping (SPM2) system. Regions of interest were drawn manually on summated PET images with reference to coregistered MRI and were defined for the caudate head; putamen; parahippocampal region; occipital, temporal, frontal, and anterior cingulate cortices; thalamus; and cerebellum, according to our previous study (*26*). The parahippocampal region included the hippocampus, posterior part of the parahippocampal gyrus, and uncus including the amygdala. Regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

Kinetics Model of ^{18}F-FE-SPA-RQ

The 3-compartment model (3CM) with 4 first-order rate constants was used to describe the kinetics of ^{18}F-FE-SPA-RQ in the brain. The 3 compartments were defined as follows: C_P, the radioactivity concentration of unchanged radioligand in plasma (arterial input function); C_{ND}, the radioactivity concentration of nondisplaceable radioligand in the brain, including nonspecifically bound and free radioligand; and C_S, the radioactivity concentration of radioligand specifically bound to receptors. The rate constants K_1 and k_2 represent the influx and efflux rates for radioligand diffusion through the blood–brain barrier, respectively. The rate constants k_3 and k_4 are the radioligand transfers between the compartments for nondisplaceable and specifically bound radioligand. This model can be described by the following equations:

$$dC_{ND}(t)/dt = K_1C_P(t) - (k_2 + k_3)C_{ND}(t) + k_4C_S(t),$$

$$dC_S(t)/dt = k_3C_{ND}(t) - k_4C_S(t), \text{ and}$$

$$C_T(t) = C_{ND}(t)+C_S(t).$$

$C_T(t)$ is the total radioactivity concentration in a brain region measured by PET.

Calculation of ^{18}F-FE-SPA-RQ Binding Potential (BP_{ND})

^{18}F-FE-SPA-RQ binding was quantified by the indirect kinetic, simplified reference tissue model (SRTM), and ratio methods. In these methods, ^{18}F-FE-SPA-RQ bindings were expressed as BP_{ND} relative to nondisplaceable bindings (*27*). We used the cerebellum as reference brain region because of its negligible NK_1 receptor

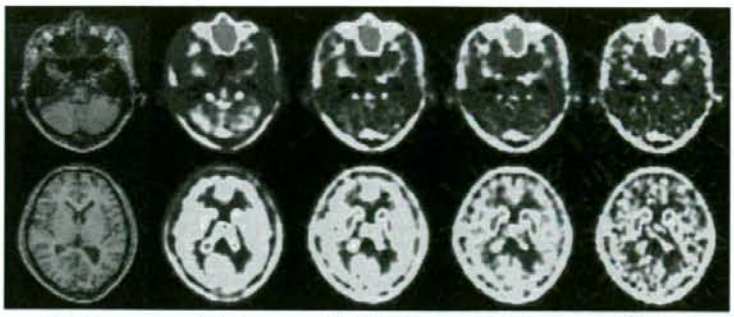

FIGURE 1. Typical summated PET images of ^{18}F-FE-SPA-RQ and T1-weighted MR images. Upper row shows slice of cerebellum, and lower row shows slice of caudate, putamen, and cerebral cortex.

density (*20,22,28*). For these analyses, the software package PMOD (PMOD Technologies) was used.

Indirect Kinetic Method. With the cerebellum as reference region, BP_{ND} can be expressed as:

$$BP_{ND} = V_{T(regions)}/V_{T(cerebellum)} - 1,$$

where $V_{T(regions)}$ is the total distribution volume ($= [K_1/k_2][k_3/k_4 + 1]$) of target regions and $V_{T(cerebellum)}$ is that of the cerebellum. K_1, k_2, k_3, and k_4 values were determined by nonlinear least-squares curve fitting to the regional time–activity curves. In this analysis, blood volume (V_b), which depends on the first-pass extraction fraction of the tracer, was assumed to be 0.04 mL/mL, with use of the radioactivity of whole blood to diminish the influence of the tracer remaining in the blood. In this study, the indirect kinetic method was used as the gold standard method (*29*).

SRTM Method. Assuming that both target and reference regions have the same level of nondisplaceable binding, the SRTM can be used to describe time–activity data in the target region as follows (*30*):

$$C_T(t) = R_1C_R(t) + (k_2 - R_1k_2/[1+BP_{ND}])C_R(t)* \exp(-k_2t/[1+BP_{ND}]),$$

where R_1 is the ratio of K_1/K_1' (K_1, influx rate constant for the brain region; K_1', influx rate constant for the reference region), $C_R(t)$ is the radioactivity concentration in the reference region (cerebellum), and * denotes the convolution integral. Using this method, 3 parameters (R_1, k_2, and BP_{ND}) were estimated by a nonlinear curve-fitting procedure. Scan data up to 180, 270, and 330 min were used.

Ratio Method. In the ratio method, BP_{ND} can be expressed as:

$$BP_{ND} = AUC_{(regions)}/AUC_{(cerebellum)} - 1,$$

where $AUC_{(regions)}$ is the area under the time–activity curve of target regions and $AUC_{(cerebellum)}$ is the time–activity curve of the cerebellum. The integration intervals of 120–180, 210–270, and 300–330 min were used.

RESULTS

Typical summated PET images of 4 time periods and T1-weighted MR images are shown in Figure 1. Typical time–activity curves in the brain showed that regional radioactivity was highest in the putamen and caudate (Fig. 2). The next highest region was the parahippocampus, followed by the cerebral cortices and thalamus. Among cerebral

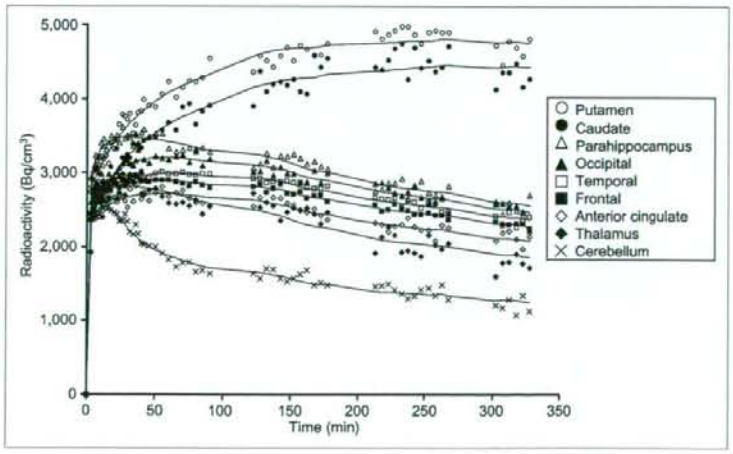

FIGURE 2. Typical time–activity curves of ^{18}F-FE-SPA-RQ in brain. Time–activity curves of all regions could be described by 3CM.

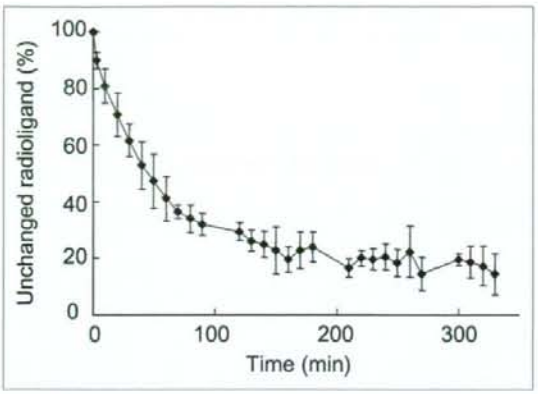

FIGURE 3. Average percentage of unchanged ^{18}F-FE-SPA-RQ in plasma. Bars indicate 1 SD.

cortices, the occipital cortex showed the highest radioactivity. Lowest radioactivity was shown in the cerebellum.

In this study, the fraction of unchanged ^{18}F-FE-SPA-RQ in plasma could not be measured by HPLC analysis in 3 of the 7 subjects because of low radioactivity in blood samples. So, the average of the fractions of unchanged ^{18}F-FE-SPA-RQ in plasma of the other 4 subjects was used for these 3 subjects for the indirect kinetic method. The average percentage fraction of unchanged ^{18}F-FE-SPA-RQ in plasma of the 4 subjects was 90.0% ± 2.9% at 3 min, 80.9% ± 6.1% at 10 min, 32.0% ± 3.9% at 90 min, 23.9% ± 5.3% at 180 min, 14.6% ± 5.9% at 270 min, and 14.4% ± 7.3% at 330 min (Fig. 3).

The rate constants for the 9 regions determined by the kinetic approach using the 3CM with arterial input function are shown in Table 1. For the cerebellum, the 2-compartment model (2CM) without specific binding compartment was also used. Akaike information criteria of the 3CM were significantly lower than those of the 2CM in the cerebellum (290 ± 28 vs. 409 ± 25, $P < 0.0001$; paired t statistics).

The BP_{ND} values of all brain regions calculated by all methods are shown in Table 2. BP_{ND} values by the SRTM method with a scan time of 330 min showed the best correlation with those by the indirect kinetic method (r = 0.98) (Fig. 4A). The SRTM method with scan times of 270 and 180 min and the ratio method with time integration intervals of 300–330, 210–270, and 120–180 min were also in good agreement with the indirect kinetic method in BP_{ND} values (r = 0.94–0.97) (Figs. 4B and 4C; Fig. 5). The BP_{ND} values, except for the caudate and putamen by the SRTM method with a scan time of 180 min and the ratio method with a time integration interval of 120–180 min, were also in good agreement with the indirect kinetic method (SRTM, $r = 0.94$, $y = 0.70x + 0.20$; ratio method, $r = 0.94$, $y = 0.69x + 0.20$).

The BP_{ND} values determined by the kinetic approach ($= k_3/k_4$) were 4.39 ± 3.93 and 5.94 ± 3.44 in the caudate and putamen. Those in the other regions were much smaller and varied widely.

DISCUSSION

After the intravenous injection of ^{18}F-FE-SPA-RQ, radioactivity was highest in the caudate and putamen and lowest in the cerebellum. BP_{ND} values in the caudate and putamen by the indirect kinetic method were 3.15 ± 0.36 and 3.11 ± 0.66, respectively, almost the same as in the previous human PET study with ^{18}F-SPA-RQ (3.08 ± 0.48 in the caudate and 3.71 ± 1.00 in the putamen) (22). The parahippocampal region and cerebral cortices showed moderate uptake, and the occipital cortex showed the highest uptake among the cerebral cortices. The thalamus showed relatively low uptake. The uptake shown in these regions was almost the same order of progression as the uptake in previous human PET studies with ^{18}F-SPA-RQ and autoradiographic studies of the human postmortem brain

TABLE 1
Rate Constants for Each Brain Region Determined by Kinetic Approach Using 3CM with Arterial Input Function

Region	Rate constant				Total distribution volume
	K_1 (mL/mL/min)	k_2 (min^{-1})	k_3 (min^{-1})	k_4 (min^{-1})	
Putamen	0.111 ± 0.019	0.036 ± 0.016	0.081 ± 0.040	0.014 ± 0.003	21.3 ± 3.4
Caudate	0.088 ± 0.018	0.023 ± 0.018	0.061 ± 0.067	0.011 ± 0.005	21.5 ± 1.7
Parahippocampus	0.140 ± 0.023	0.033 ± 0.007	0.027 ± 0.020	0.015 ± 0.006	11.3 ± 1.4
Occipital lobe	0.127 ± 0.017	0.065 ± 0.038	0.089 ± 0.057	0.021 ± 0.007	10.0 ± 1.1
Temporal lobe	0.106 ± 0.050	0.050 ± 0.025	0.067 ± 0.038	0.020 ± 0.003	9.5 ± 0.9
Frontal lobe	0.108 ± 0.011	0.041 ± 0.011	0.052 ± 0.023	0.021 ± 0.002	9.1 ± 0.9
Anterior cingulate cortex	0.115 ± 0.014	0.064 ± 0.018	0.072 ± 0.027	0.019 ± 0.005	8.8 ± 0.9
Thalamus	0.112 ± 0.019	0.043 ± 0.018	0.038 ± 0.026	0.019 ± 0.003	7.6 ± 0.9
Cerebellum					
3CM	0.115 ± 0.017	0.051 ± 0.015	0.017 ± 0.008	0.013 ± 0.003	5.2 ± 0.4
2CM	0.089 ± 0.014	0.019 ± 0.002			4.6 ± 0.3

Values are mean ± SD. For cerebellum, both 2CM and 3CM were applied.

TABLE 2
BP_{ND} Values for Each Brain Region with All Methods

Region	Method						
		SRTM (min)			Ratio (min)		
	Indirect kinetic	330	270	180	300–330	210–270	120–180
Putamen	3.11 ± 0.66	2.43 ± 0.33	2.33 ± 0.32	2.20 ± 0.27	2.62 ± 0.40	2.25 ± 0.28	1.81 ± 0.19
Caudate	3.15 ± 0.36	2.14 ± 0.24	2.02 ± 0.22	1.91 ± 0.20	2.31 ± 0.40	1.98 ± 0.26	1.57 ± 0.17
Parahippocampus	1.17 ± 0.25	1.04 ± 0.16	1.02 ± 0.12	1.01 ± 0.12	1.11 ± 0.22	1.05 ± 0.16	1.03 ± 0.20
Occipital lobe	0.94 ± 0.23	0.88 ± 0.14	0.92 ± 0.07	0.90 ± 0.13	0.97 ± 0.16	0.94 ± 0.16	0.95 ± 0.17
Temporal lobe	0.82 ± 0.15	0.77 ± 0.11	0.79 ± 0.08	0.78 ± 0.11	0.85 ± 0.15	0.83 ± 0.15	0.79 ± 0.15
Frontal lobe	0.76 ± 0.15	0.72 ± 0.12	0.74 ± 0.07	0.73 ± 0.11	0.79 ± 0.17	0.76 ± 0.15	0.75 ± 0.15
Anterior cingulate cortex	0.69 ± 0.16	0.66 ± 0.15	0.67 ± 0.13	0.71 ± 0.17	0.70 ± 0.16	0.69 ± 0.13	0.67 ± 0.13
Thalamus	0.46 ± 0.14	0.46 ± 0.13	0.51 ± 0.10	0.49 ± 0.14	0.45 ± 0.12	0.45 ± 0.13	0.49 ± 0.16

Values are mean ± SD.

(*20,22,28*). In a previous autoradiographic study using ^{3}H-GR205171, the maximum number of binding sites for NK_1 receptor in the striatum was 6 times as much as in the cortex (*31*), a result in accordance with the BP_{ND} values in these regions in the present study.

In this study, the indirect kinetic method with arterial blood sampling was used as the gold standard method, because BP_{ND} determined by the kinetic approach as k_3/k_4 showed wide variation. The BP_{ND} values in all brain regions determined by the SRTM method (with scan times of 330, 270, and 180 min) and by the ratio method (with time integration intervals of 300–330, 210–270, and 120–180 min) were in good agreement with those determined by the indirect kinetic method. Although good correlations were observed in BP_{ND} values among the methods, BP_{ND} was underestimated in the caudate and putamen using the

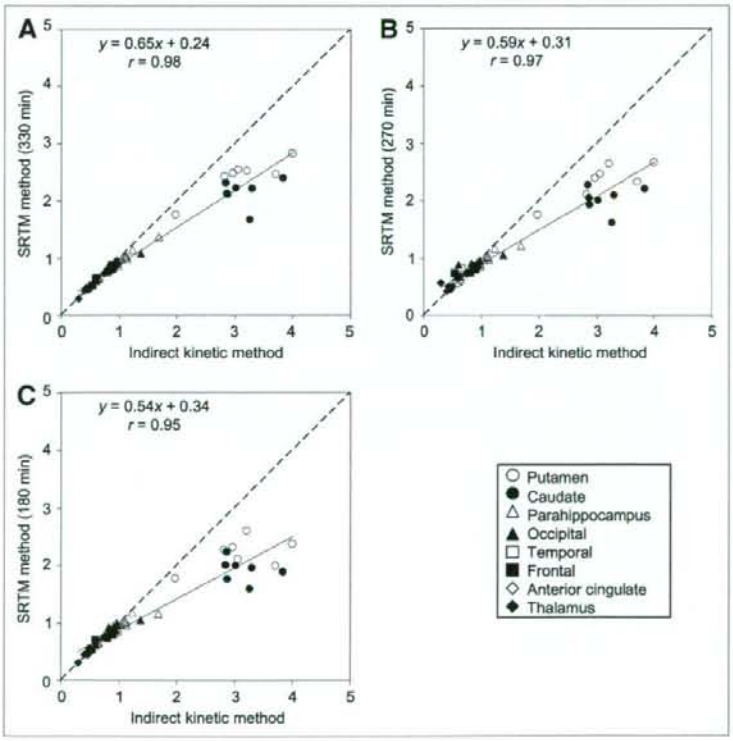

FIGURE 4. Correlation among BP_{ND} values in all brain regions estimated by indirect kinetic and SRTM methods, with scan times of 330 (A), 270 (B), and 180 (C) min.

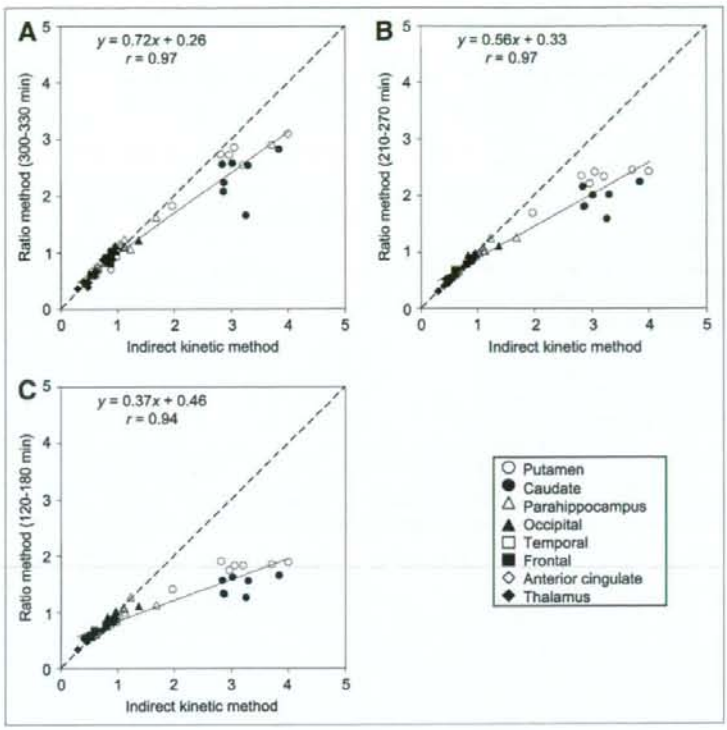

FIGURE 5. Correlation among BP_{ND} values in all brain regions estimated by indirect kinetic and ratio methods, with time integration intervals of 300–330 (A), 210–270 (B), and 120–180 (C) min.

SRTM and ratio methods. The underestimations of BP_{ND} were 32% and 34% in the caudate and 22% and 16% in the putamen for the SRTM method (with a scan time of 330 min) and the ratio method (with a time integration interval of 300–330 min), respectively. More underestimation was observed in the caudate and putamen with the shorter scan time in the SRTM method and with the earlier time integration interval in the ratio method. The reason might be that striatal radioactivity in some subjects did not reach a peak by 330 min. However, the BP_{ND} values of the other regions calculated by the SRTM method (with a scan time of 180 min) and the ratio method (with a time integration interval of 120–180 min) were not greatly underestimated, indicating that the scan time can be shortened to 180 min. Although the indirect kinetic method was considered as the gold standard method, it required a long PET time and arterial blood sampling, an invasive procedure sometimes difficult for patients with psychiatric disorders. The ratio method, which does not require a long PET scanning time and arterial blood sampling, would surely be preferable for clinical investigations. The ratio method, with a time integration interval of 300–330 min, seemed most suitable because the correlation coefficient with the indirect kinetic method was highest and the slope of the regression line was nearest to 1.

The time–activity curves in the cerebellum were well described by the 3CM rather than the 2CM. Similar results were reported for several PET radioligands, with the kinetics in the reference region also being evaluated using the 3CM (*29,32,33*). The results could be explained if the cerebellum would contain specific bindings for NK_1 receptors. However, previous autoradiographic studies showed that the density of NK_1 receptors in the cerebellum was low (*22*), and a previous PET study with ^{18}F-SPA-RQ showed that there was no change in the cerebellar signal before and after high blocking doses of the NK_1 receptor antagonist aprepitant (*20*). Another possible explanation for the results was that the compartments of free and nonspecific binding might have been separated by the kinetic analysis. In addition, ^{18}F-FE-SPA-RQ showed defluorination during the later scans, and bone uptake of ^{18}F might influence the radioactivity in the cerebral cortex and cerebellum adjacent to the skull (although ^{18}F-FE-SPA-RQ showed reduced radioactive accumulation in bone, compared with ^{18}F-SPA-RQ (*23*)).

CONCLUSION

^{18}F-FE-SPA-RQ is a suitable radioligand for PET measurement of NK_1 receptors in the human brain. The 3CM could well describe the brain kinetics of ^{18}F-FE-SPA-RQ. Because the ratio method does not require long scanning times and arterial blood sampling, this method would be useful for clinical research on psychiatric disorders.

ACKNOWLEDGMENTS

We thank Dr. Fumitoshi Kodaka, Dr. Tatsui Otsuka, Katsuyuki Tanimoto, Takahiro Shiraishi, and Akira Ando for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator. This study was supported by a consignment expense for the Molecular Imaging Program on Research Base for PET Diagnosis from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government.

REFERENCES

1. Baker KG, Halliday GM, Hornung JP, Geffen LB, Cotton RG, Tork I. Distribution, morphology and number of monoamine-synthesizing and substance P-containing neurons in the human dorsal raphe nucleus. *Neuroscience.* 1991; 42:757–775.
2. Nicholas AP, Pieribone VA, Arvidsson U, Hokfelt T. Serotonin-, substance P- and glutamate/aspartate-like immunoreactivities in medullo-spinal pathways of rat and primate. *Neuroscience.* 1992;48:545–559.
3. Sergeyev V, Hokfelt T, Hurd Y. Serotonin and substance P co-exist in dorsal raphe neurons of the human brain. *Neuroreport.* 1999;10:3967–3970.
4. Vincent SR, Satoh K, Armstrong DM, Panula P, Vale W, Fibiger HC. Neuropeptides and NADPH-diaphorase activity in the ascending cholinergic reticular system of the rat. *Neuroscience.* 1986;17:167–182.
5. Masu Y, Nakayama K, Tamaki H, Harada Y, Kuno M, Nakanishi S. cDNA cloning of bovine substance-K receptor through oocyte expression system. *Nature.* 1987;329:836–838.
6. Nakanishi S. Mammalian tachykinin receptors. *Annu Rev Neurosci.* 1991; 14:123–136.
7. Ding YQ, Shigemoto R, Takada M, Ohishi H, Nakanishi S, Mizuno N. Localization of the neuromedin K receptor (NK_3) in the central nervous system of the rat. *J Comp Neurol.* 1996;364:290–310.
8. Nakaya Y, Kaneko T, Shigemoto R, Nakanishi S, Mizuno N. Immunohistochemical localization of substance P receptor in the central nervous system of the adult rat. *J Comp Neurol.* 1994;347:249–274.
9. Snider WD, McMahon SB. Tackling pain at the source: new ideas about nociceptors. *Neuron.* 1998;20:629–632.
10. Sanger GJ. Neurokinin NK_1 and NK_3 receptors as targets for drugs to treat gastrointestinal motility disorders and pain. *Br J Pharmacol.* 2004;141:1303–1312.
11. Kincy-Cain T, Bost KL. Increased susceptibility of mice to Salmonella infection following in vivo treatment with the substance P antagonist, spantide II. *J Immunol.* 1996;157:255–264.
12. Metwali A, Blum AM, Elliott DE, Setiawan T, Weinstock JV. Cutting edge: hemokinin has substance P-like function and expression in inflammation. *J Immunol.* 2004;172:6528–6532.
13. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer.* 2003; 39:1074–1080.
14. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol.* 2003;21:4112–4119.
15. de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol.* 2003;21:4105–4111.
16. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science.* 1998;281:1640–1645.
17. Kramer MS, Winokur A, Kelsey J, et al. Demonstration of the efficacy and safety of a novel substance P (NK_1) receptor antagonist in major depression. *Neuropsychopharmacology.* 2004;29:385–392.
18. Keller M, Montgomery S, Ball W, et al. Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry.* 2006;59:216–223.
19. Solin O, Eskola O, Hamill TG, et al. Synthesis and characterization of a potent, selective, radiolabeled substance-P antagonist for NK_1 receptor quantitation: ([^{18}F]SPA-RQ). *Mol Imaging Biol.* 2004;6:373–384.
20. Bergstrom M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol Psychiatry.* 2004;55:1007–1012.
21. Hargreaves R. Imaging substance P receptors (NK_1) in the living human brain using positron emission tomography. *J Clin Psychiatry.* 2002;63(suppl 11):S18–S24.
22. Hietala J, Nyman MJ, Eskola O, et al. Visualization and quantification of neurokinin-1 (NK_1) receptors in the human brain. *Mol Imaging Biol.* 2005; 7:262–272.
23. Hamill T, Ryan C, Krause S, et al. The synthesis and in vivo characterization of [^{18}F]FESPARQ, a neurokinin-1 (NK_1) receptor PET ligand [abstract]. *J Labelled Comp Radiopharm.* 2003;46(suppl 1):S35.
24. Haneda E, Higuchi M, Maeda J, et al. In vivo mapping of substance P receptors in brains of laboratory animals by high-resolution imaging systems. *Synapse.* 2007;61:205–215.
25. Zhang MR, Maeda J, Furutsuka K, et al. [^{18}F]FMDAA1106 and [^{18}F]FE-DAA1106: two positron-emitter labeled ligands for peripheral benzodiazepine receptor (PBR). *Bioorg Med Chem Lett.* 2003;13:201–204.
26. Ito H, Takahashi H, Arakawa R, Takano H, Suhara T. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. *Neuroimage.* 2008;39:555–565.
27. Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab.* 2007;27:1533–1539.
28. Caberlotto L, Hurd YL, Murdock P, et al. Neurokinin 1 receptor and relative abundance of the short and long isoforms in the human brain. *Eur J Neurosci.* 2003;17:1736–1746.
29. Ito H, Sudo Y, Suhara T, Okubo Y, Halldin C, Farde L. Error analysis for quantification of [^{11}C]FLB 457 binding to extrastriatal D_2 dopamine receptors in the human brain. *Neuroimage.* 2001;13:531–539.
30. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. *Neuroimage.* 1996;4:153–158.
31. Griffante C, Carletti R, Andreetta F, Corsi M. [^{3}H]GR205171 displays similar NK_1 receptor binding profile in gerbil and human brain. *Br J Pharmacol.* 2006; 148:39–45.
32. Farde L, Ito H, Swahn CG, Pike VW, Halldin C. Quantitative analyses of carbonyl-carbon-11-WAY-100635 binding to central 5-hydroxytryptamine-1A receptors in man. *J Nucl Med.* 1998;39:1965–1971.
33. Lundberg J, Odano I, Olsson H, Halldin C, Farde L. Quantification of ^{11}C-MADAM binding to the serotonin transporter in the human brain. *J Nucl Med.* 2005;46:1505–1515.