task requires that subjects not push a button when the target stimulus is presented. In degraded CPT the stimulus is covered by a pattern of mosaic dots making the image indistinct.

The CPT are also used in clinical studies. Previous studies have shown that patients with epilepsy,[2] brain tumor,[1,3] schizophrenia,[4–7] attention-deficit–hyperactivity disorder (ADHD),[8–13] anxiety disorder,[14] and dementia[15] have attention function deficits.

Several studies have examined the development of attention function in healthy children. Lin *et al.* examined the relationships of age and sex with CPT performance in 341 schoolchildren aged 6–15 years using degraded CPT and CPT-AX.[16] They found that CPT performance parameters (hit rate, false alarm rate, and sensitivity index [d']) exhibited quadratic relationships with age. Sex was associated with hit rate and sensitivity only in testing with degraded CPT. These authors also showed that sustained attention develops during primary school age. Greenberg and Waldman used TOVA (a task similar to CPT-X) in 775 subjects aged 6–16 years to obtain normative developmental data, and found that attention and impulse control develop in a non-linear fashion, first rapidly during early childhood, with a subsequent leveling off during later childhood and adolescence.[17] Conners *et al.* examined normative data for 816 children aged 9–17 years using CPT-notX, and reported that systematic main effects of improved performance at an older age were found for all variables, including reaction time (RT), RT standard error, omission errors, commission errors, and d'.[18] Significant gender effects included more impulsive errors, less variability, and faster RT for boys, with no interactions between age and gender. Chen *et al.* examined the CPT performance of 115 adolescents (junior high school students; mean age ± SD, 14.0 ± 13.0 years) and 345 adults (mean age, 41.3 ± 13.0 years) using degraded CPT and CPT-AX.[19] Their results showed that older age was associated with decreasing hit rate and sensitivity (d'). Men had a higher hit rate and d' than women on degraded CPT.

Further, a recent study combined use of the electroencephalogram (EEG) and CPT in an examination of children aged 9–11 years[20] and normal adults.[21] Studies involving the use of event-related potentials (ERP) and CPT in children aged 12–17 years[22] have also been reported.

The goal of the present study was to measure the development of cognitive and attention functions in children on CPT. CPT can be used to objectively assess cognitive function along with attention. In developmental studies it is necessary to assign the same task to sufficiently large numbers of children over a wide age range. Because the most useful task is one that can be performed by young children, CPT-X was chosen as a comparatively easy one to perform. In addition, it has been reported that CPT can objectively assess abnormalities related to attention function in children with ADHD.[23,24] We believe that normalized CPT data will be helpful in evaluating ADHD and other attention-related disorders.

METHODS

Subjects

This study involved 541 healthy Japanese girls. Individuals with a history of psychiatric disorder were excluded from the study. The study procedure was orally explained to the children and their parents, and informed consent was obtained from the parents. In the present study we assessed data for girls alone in order to exclude effects of sex. The CPT data for children who completed the entire task were used for statistical analysis. Data with a total error >2SD were excluded (numbers of excluded subjects: 5 years, $n = 1$; 6 years, $n = 1$; 7 years, $n = 4$; 8 years, $n = 4$; 9 years, $n = 3$; 10 years, $n = 5$; 11 years, $n = 3$; 12 years, $n = 2$). Finally, the data of 518 subjects aged 5–12 years (numbers of subjects: 5 years, $n = 35$; 6 years, $n = 42$; 7 years, $n = 78$; 8 years, $n = 82$; 9 years, $n = 86$; 10 years, $n = 88$; 11 years, $n = 80$; 12 years, $n = 27$) were analyzed. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tamagawa University.

Procedure

The stimuli of the CPT-X task were visually presented on a cathode-ray tube (CRT) screen controlled by a Windows PC loaded with original software (Continuous Performance Test for Windows Ver.2; Tokyo Medical Dental University, Tokyo, Japan). The stimuli appeared 400 times in a circle approximately 7 cm in diameter and situated at the center of a monitor at a distance of 50 cm from the subject. The visual stimuli in CPT included numerals from 1 to 9. The subject was required to push a button quickly when the target, defined as the number 7, appeared.

Stimuli were randomly presented in order to avoid effects of expectation. The inter-stimulus interval was set within a range of 1500 ± 500 ms. The percentage of targets was 20% (80 out of 400 times). Total experimental time was 13 min and 20 s. Prior to data acquisition the task procedure was fully explained to the subjects, and they were given sufficient practice to understand it.

Parameters of measurement

The following 10 parameters were measured.

The number of cancellations of a target stimulus (T-cancel) was the number of times a subject responded within 150 ms of target presentation onset. The number of cancellations of a non-target stimulus (N-cancel) was the number of times a subject responded within 150 ms of non-target stimulus presentation onset. The shortest response time for detecting the target stimuli is said to be 150 ms.

The number of omission errors (Omission) was the number of times a subject failed to respond to a target stimulus. Hit rate (Hit) was the ratio of accurate responses to the total number of times a target stimulus was presented, and was calculated as (80 – number of cancelled targets – omission errors)/80.

The number of commission errors (Commission) was the number of times a subject responded to a non-target stimulus. The false alarm rate (False) was the ratio of mis-responses to the total number of non-target stimuli, and was calculated as (number of cancelled non-target stimuli + commission errors)/320.

Mean RT for a correct response was the time from presentation of the target stimulus to the reaction. The coefficient of variance of mean reaction time (CVRT) was also determined.

The sensitivity index (d') reflects a subject's perceptual sensitivity to a target; it is the distance between signal and noise distributions in standard score units, calculated as z(h) – z(f) with z, h, and f equal to normal deviance, hit rate, and false alarm rate, respectively. High d' indicate high levels of signal detection relative to noise and suggest better discrimination between target and non-target stimuli.

The response criterion index (lnβ) is a function of a subject's tendency to respond too little or too much relative to the actual distribution of a target, and is calculated as $\ln\{y[z(h)]/y[z(f)]\}$, with y the ordinate of the normal distribution. A lnβ of 1 indicates the smallest bias in responding. A lnβ <1 indicates that a subject tends to respond to noise (non-target) as a target, while a lnβ >1 indicates that he or she tends to respond to the target as noise (non-target).

Statistical analysis

Data were analyzed using the statistical software package SPSS 11.5 J for Windows (SPSS Inc., Chicago, IL, USA). The relationship between age and CPT measurements was examined using one-way analysis of variance (ANOVA) and post-hoc Scheffe's analysis. The significance level was set at $P < 0.05$ (two-tailed).

RESULTS

Tables 1 and 2 show mean scores of CPT indexes by age groups from 5 to 12 years of age.

Cancellation of target and non-target stimuli

There were significant differences in number of cancellations of target stimuli (T-cancel) among the age groups. A post-hoc test showed that T-cancel was significantly higher in the 5-year-old group than in the other age groups. Results for T-cancel exhibited significant change until 5 years of age.

There were also significant differences in number of cancellations of non-target stimuli (N-cancel) among the age groups. A post-hoc test showed that N-cancel was significantly higher in the 5-year-old group than in the other age groups, and significantly higher in the 6-year-old group than in the 9–11-year-old groups. Results for N-cancel exhibited significant change until 6 years of age.

Hit rate, false alarm rate, and omission and commission errors

As shown in Table 1, there were significant differences in hit rate (Hit) among the age groups. A post-hoc test showed that Hit was significantly lower in the 5-year-old groups than in the 6–12-year-old groups, and in the 6-year-old group than in the 7–12-year-old groups. Results for Hit exhibited significant change until 6 years of age.

There were also significant differences in False alarm rate (False) among the age groups. A post-hoc test showed that False was significantly higher in the

Table 1 CPT accuracies (mean ± SD) by age group (5–12 years)

	CPT indexes					
	T-cancel	N-cancel	Hit	False	Omission	Commission
5 years (n = 35)	4.77 ± 9.36[a]	19.14 ± 38.29[a]	0.66 ± 0.23[a]	0.01 ± 0.02[a]	22.74 ± 16.45[a]	2.89 ± 4.25[a]
6 years (n = 42)	1.67 ± 1.57[b]	9.14 ± 6.19[b]	0.81 ± 0.12[b]	0.01 ± 0.01[b]	13.29 ± 8.65[b]	1.62 ± 2.00[a,c]
7 years (n = 78)	0.06 ± 0.89[b]	2.82 ± 3.36[b,c]	0.96 ± 0.04[c]	0.00 ± 0.00[b]	2.24 ± 2.48[c]	1.46 ± 1.48[b,c]
8 years (n = 82)	0.38 ± 0.64[b]	2.10 ± 2.25[b,c]	0.98 ± 0.03[c]	0.00 ± 0.00[b]	1.52 ± 2.05[c]	0.90 ± 1.22[b,c]
9 years (n = 86)	0.26 ± 0.49[b]	1.23 ± 1.83[c]	0.98 ± 0.02[c]	0.00 ± 0.01[b]	1.27 ± 1.63[c]	1.37 ± 1.82[b,c]
10 years (n = 88)	0.22 ± 0.49[b]	0.67 ± 0.93[c]	0.99 ± 0.02[c]	0.00 ± 0.00[b]	0.75 ± 1.38[c]	0.96 ± 1.10[b,c]
11 years (n = 80)	0.06 ± 0.24[b]	0.36 ± 0.90[c]	0.99 ± 0.01[c]	0.00 ± 0.00[b]	0.63 ± 1.07[c]	1.28 ± 1.56[b,c]
12 years (n = 27)	0.00 ± 0.00[b]	0.19 ± 0.40[b,c]	1.00 ± 0.01[c]	0.00 ± 0.00[b]	0.37 ± 0.74[c]	0.85 ± 1.17[b,c]
F (7,510)	16.103*	16.837*	116.580*	6.302*	104.275*	5.351*

Figures with different superscript letters in the same row differ significantly with each other at $P < 0.05$. (*$P < 0.05$). n, the number of subjects; T-cancel, the number of cancellations of the target stimuli; N-cancel, the number of cancellations of the non-target stimuli; Hit, hit rate; False, false alarm rate; Omission, the number of omission errors; Commission, the number of commission errors.

Table 2 CPT responses (mean ± SD) by age group (5–12 years)

	CPT indexes			
	RT	CVRT	d′	lnβ
5 years (n = 35)	769.11 ± 57.74[a]	35.34 ± 27.22[a]	2.17 ± 1.15[a]	1.22 ± 0.47[a]
6 years (n = 42)	737.02 ± 53.22[a]	22.94 ± 6.09[b]	2.87 ± 0.67[b]	1.27 ± 0.36[a]
7 years (n = 78)	623.41 ± 68.84[b]	18.79 ± 3.91[b,c]	4.26 ± 0.67[c]	0.86 ± 0.67[a]
8 years (n = 82)	598.74 ± 66.20[b,c]	17.81 ± 3.44[b,c]	4.51 ± 0.57[c,g,i,k]	0.83 ± 0.68[a]
9 years (n = 86)	551.42 ± 59.92[d]	18.00 ± 3.79[b,c]	4.62 ± 0.54[d,i,k]	0.88 ± 0.77[a]
10 years (n = 88)	518.94 ± 55.95[d,c,b]	17.73 ± 3.72[b,c]	4.82 ± 0.39[d,h,j]	0.94 ± 0.70[a]
11 years (n = 80)	418.68 ± 52.43[f]	16.22 ± 3.36[c]	4.88 ± 0.38[c,f,h,i]	0.87 ± 0.63[a]
12 years (n = 27)	483.37 ± 61.10[c,f,g,h]	17.15 ± 3.13[b,c]	5.00 ± 0.31[d,f,g]	0.93 ± 0.48[a]
F (7,510)	153.815*	24.755*	132.438*	3.248*

Figures with different superscript letters in the same row differ significantly with each other at $P < 0.05$. (*$P < 0.05$). RT, mean reaction time for a correct response; CVRT, coefficient of variance of mean reaction time for a correct response; d′, the sensitivity index; and lnβ, the response criterion index.

5-year-old group than in the other age groups. Results for False exhibited significant change in 5 years of age.

There were significant differences in number of omission errors (Omission) among the age groups. A post-hoc test showed that Omission was significantly higher in the 5-year-old group than in the 6–12-year-old groups, and in 6-year-old group than in the 7–12-year-old groups. Results for Omission exhibited significant change until 6 years of age.

There were also significant differences in number of commission errors (Commission) among the age groups. A post-hoc test showed that Commission was significantly higher in the 5-year-old group than in the 7–12-year-old groups. Results for Commission exhibited significant change in 5 years of age.

Reaction time for correct responses and its coefficient of variance

As shown in Table 2, there were significant differences in mean RT for a correct response among the age groups. A post-hoc test showed that RT was significantly longer in the 5-year-old group than in the 7–12-year-old groups, in the 6-year-old group than in the 7–12-year-old groups, in the 7-year-old group

than in the 9–12-year-old groups, in the 8-year-old group than in the 9–12-year-old groups, in the 9-year-old group than in the 11–12-year-old groups, and in the 10-year-old group than in the 11-year-old group. Results for RT exhibited significant change until 11 years of age.

There were also significant differences in the CVRT for a correct response among the age groups. A post-hoc test showed that CVRT was significantly larger in the 5-year-old group than in the other age groups, and significantly larger in the 6-year-old group than in the 11-year-old group. Results for CVRT exhibited significant change until 6 years of age.

d′ and lnβ

As shown in Table 2, there were significant differences in d′ among age groups. A post-hoc test showed that d′ was significantly lower in the 5-year-old than in the other age groups, in the 6-year-old group than in the 7- to 12-year-old groups, in the 7-year-old group than in the 9- to 12-year-old groups, and in the 8-year-old group than in the 11-year-old group. Results for d′ exhibited significant change until 8 years of age.

There were also significant differences in lnβ among the age groups, though no significant differences in it were noted between groups on post-hoc testing.

DISCUSSION

In the present study, we examined the development of cognitive and attention functions in healthy children using the CPT-X task. We examined a sufficient number of subjects and evaluated a number of indexes to enable easy comparison with findings of previous studies.

The number of cancellations of either the target stimulus (T-cancel) or non-target stimulus (N-cancel) is an index related to the visual recognition of stimuli in a particular CPT. It is believed that this response is based on prediction. In the present study, T-cancel events decreased at the age of 5 years and N-cancel events decreased at the ages of 5 and 6 years, suggesting that development of inhibition of prediction response occurs at these ages.

Failure to control responses to non-target stimuli causes commission errors (Commission) and higher false alarm rates (False), reflecting lack of response inhibition. Previous studies reported that Commission decreased with age.[16–18] Consistent with the results of these studies, in our study Commission decreased significantly at 5 years of age and remained constant thereafter. The development of response inhibition thus appears to reach a plateau at an early age.

The CVRT for correct responses indicates the degree of stability of processing time. This stability improves significantly at 5 and 6 years of age. Thus, the stability of processing time for correct responses also reaches a plateau at an early age.

High numbers of omission errors (Omission) and lower hit rates (Hit) occur due to inattention to target responses. Greenberg and Waldman, and Conners *et al.* showed that Omission decreased with increase in age.[17,18] Further, Lin *et al.* showed that attention function develops during the primary school period.[16] But in the present study Omission decreased more sharply and at a younger age than in the study by Lin *et al.* We thus believe that inattention decreases markedly at these ages.

The mean RT for correct responses includes the processing time from presentation of the target stimulus to reaction. Previous studies using CPT for healthy young subjects showed that RT decreased with age.[16–18] In the present study, RT decreased markedly until 11 years of age.

The sensitivity index d′, developed by signal detection theory,[25] measures discrimination between signal and noise. In the present study d′ increased rapidly up to the age of 8 years. In particular, the rate of change in d′ was very large in children between the age of 6 and 7 years. Lin *et al.* and Conners *et al.* reported that d′ increased with increase in age.[16,18] The present findings are consistent with the results of these studies. Discrimination ability thus appears to increase rapidly until the age of 8 years.

The results of previous studies on the response criterion index lnβ[16,18,19] cannot be directly compared with our own due to differences in task style. This index indicates a subject's tendency to respond too little or too much relative to the actual distribution of task stimuli. Hence, if a subject executes the task correctly, his or her lnβ should be close to 1. In the present study a tendency toward noise reduction was observed in children aged 5 and 6 years, while a tendency toward improved signal detection ability was observed in children older than 7 years of age.

These findings indicate that several response abilities measured by CPT exhibit differences by age. The parameters were correspondingly divided into three

types based on pattern of change: T-cancel, False, and Commission, which are related to inhibition of response; N-cancel, Hit, Omission, which are related to inattention to stimuli; and CVRT, which is related to stability of processing time, all exhibited significant change until 5 or 6 years of age. d', which is related to ability to discriminate between target and non-target, exhibited significant change until 8 years of age. RT, which is related to processing time, exhibited significant change until 11 years of age. Thus, inhibition function, inattention, and stability of processing time develop first. Subsequently, discrimination ability increases based on these developments, and finally processing time is reduced.

One limitation of the present study is its inclusion of female subjects alone. Several studies have demonstrated sex-related differences in CPT performance. Lin *et al.* and Chen *et al.* reported that girls had a lower hit rate, lower d', and higher lnβ than boys.[16,19] In contrast, Conners *et al.* reported that girls had lower omission errors, higher d', and lower lnβ than boys.[18] These reports indicate that findings regarding gender differences in development of attention function are still inconclusive.

We included 5-year-old children in the present study. Although this age group is believed to still have poor conceptual understanding of figures, CPT was a practicable task because the subjects could discriminate between the shapes of the target stimuli. The poor performance of this low-age group is believed to be due to immaturity of attention function and not to poor conceptual understanding of figures.

In conclusion, we assessed CPT-X indexes by age in order to examine the development of cognitive and attention functions during childhood. The findings indicate that development of cognitive and attention functions during childhood can be tracked using CPT parameters. At the age of 5 and 6 years, in particular, marked changes were observed in inhibition function, inattention, and stability of processing time, which are related to abilities to respond. In addition, discrimination ability changed up to approximately 8 years of age. Finally, processing time decreased up to approximately 11 years of age. These normalized CPT data should be useful in evaluating ADHD and other attention-related disorders.

ACKNOWLEDGMENTS

We thank Professor Makoto Uchiyama of the Department of Neuropsychiatry, Nihon University School of Medicine, and Professor Gert Hauske of the Munich University of Technology for reading the manuscript and for providing helpful suggestions. We gratefully acknowledge the contributions of Dr Hiroshi Sasaki and Dr Jiro Okuda of the Tamagawa University Brain Science Institute, and Mr Akemi Kazuno of Shirayuri Kindergarten. This work was supported by the 21st Century COE Program of the Japanese Ministry of Education, Culture, Sports, and Technology.

REFERENCES

1 Rosvold HE, Mirsky AF, Sarason I, Bransome ED Jr, Beck LH. A continuous performance test of brain damage. *J. Consult. Clin. Psychol.* 1956; **20**: 343–350.
2 Mirsky AF, Primac DW, Marsan CA, Rosvold HE, Stevens JR. A comparison of the psychological test performance of patients with focal and nonfocal epilepsy. *Exp. Neurol.* 1960; **2**: 75–89.
3 Merchant TE, Kiehna EN, Miles MA, Zhu J, Xiong X, Mulhern RK. Acute effects of irradiation on cognition: Changes in attention on a computerized continuous performance test during radiotherapy in pediatric patients with localized primary brain tumors. *Int. J. Radiat. Oncol. Biol. Phys.* 2002; **53**: 1271–1278.
4 Buchanan RW, Strauss ME, Breier A, Kirkpatrick B, Carpenter WT Jr. Attentional impairments in deficit and nondeficit forms of schizophrenia. *Am. J. Psychiatry* 1997; **154**: 363–370.
5 Liu SK, Hwu HG, Chen WJ. Clinical symptom dimensions and deficits on the continuous performance test in schizophrenia. *Schizophr. Res.* 1997; **25**: 211–219.
6 Nieuwenstein MR, Aleman A, Haan EHF. Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: A meta-analysis of WCST and CPT studies. *J. Psychiatr. Res.* 2001; **35**: 119–125.
7 Suwa H, Matsushima E, Ohta K, Mori K. Attention disorders in schizophrenia. *Psychiatry Clin. Neurosci.* 2004; **58**: 249–256.
8 Halperin JM, Wolf L, Greenblatt ER, Young G. Subtype analysis of commission errors on the continuous performance test in children. *Dev. Neuropsychol.* 1991; **7**: 207–217.
9 Harper GW, Ottinger DR. The performance of hyperactive and control preschoolers on a new computerized measure of visual vigilance: The preschool vigilance task. *J. Child Psychol. Psychiatry* 1992; **33**: 1365–1392.
10 Russell AB, Gail MG. Are tests of frontal lobe functions useful in the diagnosis of attention deficit disorders? *Clin. Neuropsychol.* 1994; **8**: 121–139.
11 Fischer M, Newby RF, Gordon M. Who are the false negatives on continuous performance tests? *J. Clin. Child Psychol.* 1995; **24**: 427–433.

[12] Cameron SC, Penelope K, Marc C, Cherise N, Virginia W. Abnormal processing of irrelevant information in attention deficit hyperactivity disorder. *Psychiatry Res.* 1995; 56: 59–70.
[13] Levin ED, Conners CK, Sparrow E *et al.* Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychophamarcology (Berl)* 1996; 123: 55–63.
[14] Baving L, Rellum T, Laucht M, Schmidt MH. Attentional enhancement to NoGo stimuli in anxious children. *J. Neural. Transm.* 2004; 111: 985–999.
[15] Alexander DA. Attention dysfunction in senile dementia. *Psychol. Rep.* 1973; 32: 229–230.
[16] Lin CCH, Hasio CK, Chen WJ. Development of sustained attention assessed using the continuous performance test among children 6–15 years of age. *J. Abnorm. Child Psychol.* 1999; 27: 403–412.
[17] Greenberg LM, Waldman ID. Developmental normative data on the test of variables of attention (T.O.V.A.). *J. Child Psychol. Psychiatry* 1993; 34: 1019–1030.
[18] Conners CK, Epstein JN, Angold A, Klaric J. Continuous performance test performance in a normative epidemiological sample. *J. Abnorm. Child Psychol.* 2003; 31: 555–562.
[19] Chen WJ, Hasio CK, Hasio L, Hwu H. Performance of the continuous performance test among community samples. *Schizophr. Bull.* 1998; 24: 163–174.
[20] González-Garrido AA, Gómez-Velázquez FR, Fernández-Harmony T, de Alba JL, Ruiz-Sandoval JL. Event-related brain potentials during a continuous performance test (CPT) task in normal children. *Arch. Med. Res.* 2001; 32: 214–220.
[21] Kasai K, Nakagome K, Hiramatsu K, Fukuda M, Honda M, Iwanami A. Psychophysiological index during auditory selective attention correlates with visual continuous performance test sensitivity in normal adults. *Int. J. Psychophysiol.* 2002; 45: 211–225.
[22] Friedman D, Boltri J, Vaughan H Jr, Erlenmeyer-Kimling L. Effects of age and sex on the endogenous brain potential components during two continuous performance tasks. *Soc. Psychophysiol. Res.* 1985; 22: 440–452.
[23] Yamada S. Pharmacotherapy of attention-deficit/hyperactivity disorder. *Jpn. J. Psychiatr. Treat.* 2002; 17: 35–42 (in Japanese).
[24] Ohkura Y. ADHD and sustained attention task. In: Nakane, Y (ed.). *ADHD Clinical Handbook.* Kongo Press, Tokyo, Japan, 2001; 213–222 (in Japanese).
[25] Tanner WP Jr, Swets JA. A decision-making theory of visual detection. *Psychol. Rev.* 1954; 61: 401–409.

knockout mouse (*27*). [^{125}I]IAF photolabeling of liver homogenates from wild-type (WT) and sigma-1 receptor knockout (KO) mice indeed showed the absence of sigma-1 receptor (26 kD) in the KO samples (Fig. 3A). In WT neonatal cardiac myocytes, 100 μM DMT reversibly inhibited I_{Na} by 29 ± 3% (n = 7 WT myocytes), whereas I_{Na} was reduced by only 7 ± 2% (n = 7 KO myocytes) in KO myocytes (Fig. 3C, $P < 0.002$).

Both DMT and sigma receptor ligands influence animal behavior. DMT injection induces hypermobility in rodents concurrently treated with the monoamine oxidase inhibitor pargyline (*28*), and this action is not antagonized by blockers of dopamine or serotonin receptors, but is potently inhibited by haloperidol (*28*). Although haloperidol is thought to act in part through the dopamine D_2 receptor system, it is also a potent sigma-1 receptor agonist [sigma-1 inhibition constant (K_i) = 3 nM (*29*); sigma-2 K_i = 54 nM (*29*)] when inhibiting voltage-gated ion channels (*5*, *25*). Haloperidol reduces brain concentrations of DMT (*8*) and DMT inhibits haloperidol binding in brain tissue more robustly than the dopamine agonist apomorphine (*8*). On the basis of these findings, which were discovered before sigma receptor identification, DMT has been hypothesized to act through an unknown "hallucinogen" receptor (*8*). We confirmed results (*28*) that intraperitoneal (ip) administration of DMT (2 mg per kilogram of body weight) 2 hours after pargyline (75 mg/kg, ip) injection induced hypermobility in WT mice (7025 ± 524.1 cm, n = 12 WT mice) in an open-field assay. Identical drug treatments in sigma-1 receptor KO mice had no hypermobility action (2328 ± 322.9 cm, n = 12 KO mice, $P < 0.0001$; Fig. 4, A and B). This result is particularly important to our understanding of sigma-1 receptor biological function because the KO mice are viable and fertile (*27*). The sigma-1 receptor dependence of DMT-induced hypermobility parallels that induced by the sigma-1 receptor ligand (+)-SKF10047 in WT but not in KO mice (*27*). As a positive control, methamphetamine, which is thought to act through catecholaminergic systems, induced hypermobility in both WT and KO mice (3 mg/kg, ip, n = 6 mice; Fig. 4, B and C) with a reduced onset rate compared with that seen for DMT (Fig. 4, A and C). This indicates that behavioral actions of DMT depend on the sigma-1 receptor, which may provide an alternative research area for psychiatric disorders that have not been linked to dopamine or *N*-methyl-D-aspartate systems.

The binding, biochemical, physiological, and behavioral studies reported here all support the hypothesis that DMT acts as a ligand for the sigma-1 receptor. On the basis of our binding results and the sigma-1 receptor pharmacophore, endogenous trace amines and their *N*-methyl and *N,N*-dimethyl derivatives are likely to serve as endogenous sigma receptor regulators. Moreover, DMT, the only known mammalian *N,N*-dimethylated trace amine, can activate the sigma-1 receptor to modulate Na^+ channels. The recent discovery that the sigma-1 receptor functions as a molecular chaperone (*30*) may be relevant, because sigma-1 receptors, which are observed in the endoplasmic reticulum, associate with plasma membrane Kv 1.4 channels (*22*) and may serve as a molecular chaperone for ion channels. Furthermore, the behavioral effect of DMT may be due to activation or inhibition of sigma-1 receptor chaperone activity instead of, or in addition to, DMT/sigma-1 receptor modulation of ion channels. These studies thus suggest that this natural hallucinogen could exert its action by binding to sigma-1 receptors, which are abundant in the brain (*1*, *27*). This discovery may also extend to *N,N*-dimethylated neurotransmitters such as the psychoactive serotonin derivative *N,N*-dimethylserotonin (bufotenine), which has been found at elevated concentrations in the urine of schizophrenic patients (*10*). The finding that DMT and sigma-1 receptors act as a ligand-receptor pair provides a long-awaited connection that will enable researchers to elucidate the biological functions of both of these molecules.

References and Notes

1. T. Hayashi, T. P. Su, *CNS Drugs* **18**, 269 (2004).
2. P. Bouchard *et al.*, *Eur. J. Neurosci.* **7**, 1952 (1995).
3. T. P. Su, A. D. Weissman, S. Y. Yeh, *Life Sci.* **38**, 2199 (1986).
4. T. P. Su, E. D. London, J. H. Jaffe, *Science* **240**, 219 (1988).
5. R. A. Wilke *et al.*, *J. Physiol.* **517**, 391 (1999).
6. R. A. Glennon *et al.*, *J. Med. Chem.* **37**, 1214 (1994).
7. F. F. Moebius, R. J. Reiter, M. Hanner, H. Glossmann, *Br. J. Pharmacol.* **121**, 1 (1997).
8. S. A. Barker, J. A. Monti, S. T. Christian, *Int. Rev. Neurobiol.* **22**, 83 (1981).
9. F. Franzen, H. Gross, *Nature* **206**, 1052 (1965).
10. M. S. Jacob, D. E. Presti, *Med. Hypotheses* **64**, 930 (2005).
11. J. Axelrod, *Science* **134**, 343 (1961).
12. J. M. Saavedra, J. Axelrod, *Science* **175**, 1365 (1972).
13. J. M. Beaton, P. E. Morris, *Mech. Ageing Dev.* **25**, 343 (1984).
14. S. A. Burchett, T. P. Hicks, *Prog. Neurobiol.* **79**, 223 (2006).
15. B. Borowsky *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 8966 (2001).
16. L. Lindemann *et al.*, *Genomics* **85**, 372 (2005).
17. J. R. Kahoun, A. E. Ruoho, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 1393 (1992).
18. A. Pal *et al.*, *Mol. Pharmacol.* **72**, 921 (2007).
19. Y. Chen, A. R. Hajipour, M. K. Sievert, M. Arbabian, A. E. Ruoho, *Biochemistry* **46**, 3532 (2007).
20. P. J. Lupardus *et al.*, *J. Physiol.* **526**, 527 (2000).
21. H. Zhang, J. Cuevas, *J. Pharmacol. Exp. Ther.* **313**, 1387 (2005).
22. E. Aydar, C. P. Palmer, V. A. Klyachko, M. B. Jackson, *Neuron* **34**, 399 (2002).
23. R. A. Wilke *et al.*, *J. Biol. Chem.* **274**, 18387 (1999).
24. C. Kennedy, G. Henderson, *Neuroscience* **35**, 725 (1990).
25. H. Zhang, J. Cuevas, *J. Neurophysiol.* **87**, 2867 (2002).
26. M. A. Johannessen, A. Ramos-Serrano, S. Ramachandran, A. E. Ruoho, M. B. Jackson, "Sigma receptor modulation of voltage-dependent sodium channels," Program No. 466.22, Annual Neuroscience Meeting, San Diego, CA, 5 November 2007.
27. F. Langa *et al.*, *Eur. J. Neurosci.* **18**, 2188 (2003).
28. P. Jenner, C. D. Marsden, C. M. Thanki, *Br. J. Pharmacol.* **69**, 69 (1980).
29. R. R. Matsumoto, B. Pouw, *Eur. J. Pharmacol.* **401**, 155 (2000).
30. T. Hayashi, T. P. Su, *Cell* **131**, 596 (2007).

31. We thank the Corinna Burger laboratory for use of their mouse behavior equipment, and A. Paul and T. Mavlyutov for providing [^{125}I]IAF and [^{125}I]-IACoc, respectively. Supported by the Molecular and Cellular Pharmacology (MCP) Graduate Program training grant from NIH T32 GM08688 and by the NIH Ruth L. Kirschstein National Research Service Award (NRSA) (F31 DA022932) from the National Institute on Drug Abuse (to D.F.). This work was funded by NIH grants R01 MH065503 (to A.E.R.) and NS30016 (to M.B.J.).

Supporting Online Material

www.sciencemag.org/cgi/content/full/323/5916/934/DC1
Materials and Methods
Fig. S1 and scheme S2
References

18 September 2008; accepted 10 December 2008
10.1126/science.1166127

When Your Gain Is My Pain and Your Pain Is My Gain: Neural Correlates of Envy and Schadenfreude

Hidehiko Takahashi,[1,2,3]* Motoichiro Kato,[4] Masato Matsuura,[2] Dean Mobbs,[5] Tetsuya Suhara,[1] Yoshiro Okubo[6]

We often evaluate the self and others from social comparisons. We feel envy when the target person has superior and self-relevant characteristics. Schadenfreude occurs when envied persons fall from grace. To elucidate the neurocognitive mechanisms of envy and schadenfreude, we conducted two functional magnetic resonance imaging studies. In study one, the participants read information concerning target persons characterized by levels of possession and self-relevance of comparison domains. When the target person's possession was superior and self-relevant, stronger envy and stronger anterior cingulate cortex (ACC) activation were induced. In study two, stronger schadenfreude and stronger striatum activation were induced when misfortunes happened to envied persons. ACC activation in study one predicted ventral striatum activation in study two. Our findings document mechanisms of painful emotion, envy, and a rewarding reaction, schadenfreude.

Envy is one of the seven biblical sins, the Shakespearian "green-eyed monster," and what Bertrand Russell (*1*) called an unfortunate facet of human nature. It is an irrational, unpleasant feeling and a "painful emotion" (*2*) characterized by feelings of inferiority and resentment produced by an awareness of another's superior quality, achievement, or possessions (*3*). Understanding envy is important because of its broad implications, ranging from individual mat-

ters to social problems. It concerns personal life satisfaction (*4*), self-evaluation/maintenance (*5*), and economic and political issues (*6–8*). We judge objects more by comparison than by their intrinsic worth and value (*9*), and self-evaluations are often derived from social comparisons with people who are self-relevant, sharing similar attributes, characteristics, group memberships, and interests (for example, gender, age, and social class) (*10*).

When envy is evoked, we often have a desire to possess the same advantage or may wish that the other lacks it (*3*). When misfortune occurs to others, emotions can manifest themselves in several ways. We can sympathize and have feelings of concern and sorrow for the other person (*11*, *12*), but we can also experience schadenfreude, a rewarding feeling derived from another's misfortune (*13*). Schadenfreude is closely related to envy, and it is more likely to arise when misfortune happens to a person who is advantaged and self-relevant than to someone who is neither advantaged nor self-relevant (*13–15*).

We investigated the brain activation associated with envy and schadenfreude. We conducted two functional magnetic resonance imaging (fMRI) studies to test two complementary hypotheses. In the first study, we hypothesized that, not only the level of possession of the person we compare ourselves with, but also the self-relevance of the comparison domain affects brain activation associated with envy through social comparison. We usually have a positive self-concept, and we experience a feeling of discomfort when we perform in a way that violates this self-concept (*16*). The anterior cingulate cortex (ACC) is activated when this positive self-concept conflicts with external information (*17*, *18*). Bearing in mind that envy is a painful emotion, we hypothesized that envy activates the dorsal ACC (dACC), where cognitive conflicts (*19*) or social pain (*12*, *20*) are processed. We predicted that dACC activation is stronger when an envied person has superior and more self-relevant possessions. In the second study, we hypothesized that a misfortune happening to an envied person produces greater brain activation associated with schadenfreude than misfortune happening to a person who is not envied. Schadenfreude should activate the ventral striatum, a central node of reward processing.

Nineteen healthy volunteers [10 men and 9 women, mean age = 22.1 ± 1.4 (SD) years] participated in the two fMRI studies. We used a scenario method as in previous social affective neuroimaging studies (*21*, *22*). Each participant was presented with a scenario in which the protagonist (oneself) and three other target persons appeared. Materials were employed from an initial survey to validate our expected results (*23*). Before the fMRI scans, we asked the participants to read and understand the scenario thoroughly and to imagine the protagonist of the scenario as themselves. In study one, we aimed to determine the level of envy in terms of whether possessions of the target person were superior or not and whether domains of comparison were self-relevant or not. In short, for male participants, the protagonist of the scenario was male and average in terms of possessions such as ability, quality, and social status. Male student A shared similar attributes with the protagonist. He possessed superior quality and ability, and the domains of comparison were important and relevant to the protagonist [superior and high relevance (SpHi)]. Female student B had different attributes and background from the protagonist. She also possessed superior quality and ability, but the domains of comparison were neither important nor relevant to the protagonist [superior and low relevance (SpLo)]. Female student C had different attributes and background from the protagonist. She possessed mediocre quality and ability, and the domains of comparison were neither important nor relevant to the protagonist [average and low relevance (AvLo)]. The scenario for male participants and profiles of the persons are shown in the appendix in (*23*). The profiles of the three target persons and comparison domains are summarized in table S1, and a schematic depiction of the stimuli and design is shown in fig. S1. We performed event-related fMRI analysis with statistical parametric mapping 2 to examine activations in response to SpHi, SpLo, and AvLo. In study two, successive misfortunes happened to student A (SpHi) and student C (AvLo) in the scenario examining reaction in response to misfortunes happening to others. A list of misfortunes is provided in table S1, and a schematic depiction of the stimuli and design is shown in fig. S2. We analyzed neural responses to misfortunes on SpHi (MisSpHi) and AvLo (MisAvLo). After the scans, the participants rated each event presented in study one in terms of how much envy they felt for the three students (i.e., 1 = no envy, 6 = extremely envious). Similarly, the participants also reported the intensity of their pleasure (schadenfreude) (1 = no pleasure, 6 = extremely pleasant) in response to misfortunes happening to students A and C in study two. That is, they gave one envy score per domain per student in study one and one schadenfreude score per misfortune per student in study two.

The self-rating results of the participants in the fMRI study were comparable to the results obtained in the initial survey. The mean values of the ratings of envy for students A, B, and C were 4.0 ± 1.0, 2.1 ± 0.8, and 1.0 ± 0.0, respectively. The mean values of schadenfreude for students A and C were

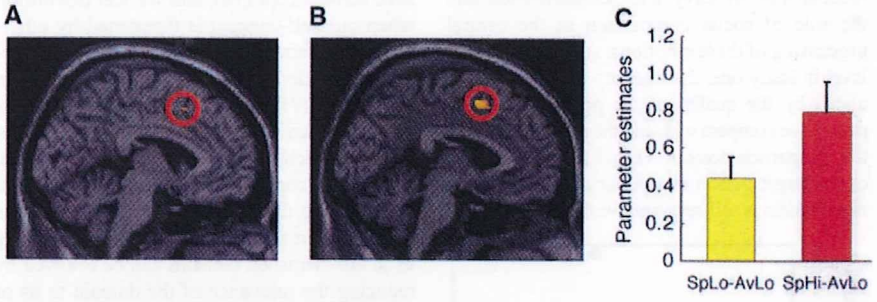

Fig. 1. Brain activation in dACC was modulated by relevance of comparison domain. Brain activations in response to **(A)** the SpLo minus AvLo condition and **(B)** the SpHi minus AvLo condition. **(C)** Mean for parameter estimates at the peak of dACC activation for SpHi-AvLo contrast (red) was greater than that for SpLo-AvLo contrast (yellow) (t = 2.56, P = 0.02). Error bars represent SE.

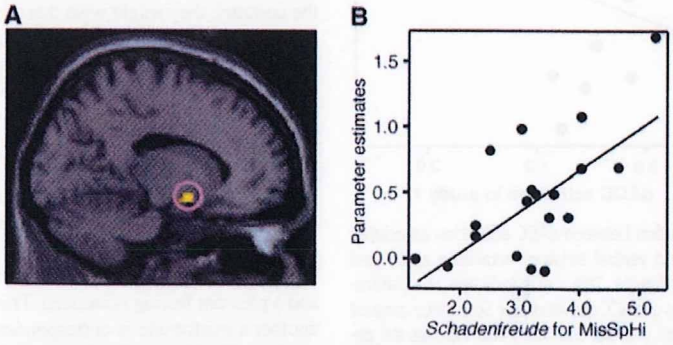

Fig. 2. Correlation between self-rating of schadenfreude and ventral striatum activation across participants. **(A)** Image showing correlation between mean rating of schadenfreude for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. **(B)** Plots and regression line of correlation (r = 0.65, P = 0.002) between schadenfreude and parameter estimates of the ventral striatum activation for MisSpHi-MisAvLo contrast at a peak voxel (–14, 2, –12).

[1]Department of Molecular Neuroimaging, National Institute of Radiological Sciences, 9-1, 4-chome, Anagawa, Inage-ku, Chiba, 263-8555, Japan. [2]Department of Life Sciences and Bioinformatics, Graduate School of Health Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku Tokyo, 113-8549, Japan. [3]Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan. [4]Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan. [5]Medical Research Council (MRC)–Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, CB2 7EF, UK. [6]Department of Neuropsychiatry, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan.

*To whom correspondence should be addressed. E-mail: hidehiko@nirs.go.jp

3.3 ± 1.0 and 1.0 ± 0.0, respectively. Self-rating scores of envy for student A were positively correlated with the magnitude of schadenfreude for student A (correlation coefficient $r = 0.50$, $P = 0.03$). Both SpHi-AvLo and SpLo-AvLo conditions produced activations in dACC, a region implicated in the processing of conflict or pain, but dACC activation was greater in the SpHi-AvLo condition ($x = -4, y = 8, z = 54$, z score = 4.07) than in the SpLo-AvLo condition ($x = -4, y = 16, z = 46$, Z score = 3.65) (Fig. 1, A to C). Regression analysis revealed positive linear correlation between self-rating scores of envy and the degree of activation in the dACC ($x = -2, y = 10, z = 52$, z score = 4.36) in SpHi-AvLo contrast (fig. S3, A and B). The MisSpHi-MisAvLo condition produced activations in the reward-related regions: the dorsal striatum (caudate, putamen) ($x = -16, y = -2, z = 16$, z score = 4.44), the ventral striatum including the nucleus accumbens ($x = -12, y = 6, z = -10$, z score = 4.41), and the medial orbitofrontal cortex ($x = -8, y = 54, z = -10$, z score = 3.46) (fig. S4, A and B). There was correlation between the intensity of schadenfreude and the degree of activation in the ventral striatum ($x = -14, y = 2, z = -12$, z score = 3.98) in MisSpHi-MisAvLo contrast (Fig. 2, A and B). dACC ($x = -2, y = 10, z = 52$) activation in SpHi-AvLo contrast was positively correlated with ventral striatum ($x = -14, y = 2, z = -12$) activation in MisSpHi-MisAvLo contrast (Fig. 3).

This study investigated the neurocognitive mechanisms of envy and schadenfreude and the role of social comparison in the central processing of these emotions. At the behavioral level in study one, the intensity of envy is modulated by the quality of the possession of the person we compare with and the self-relevance of the comparison domain. That is, if the possession of the target person is superior and the comparison domain is self-relevant, we feel intense envy.

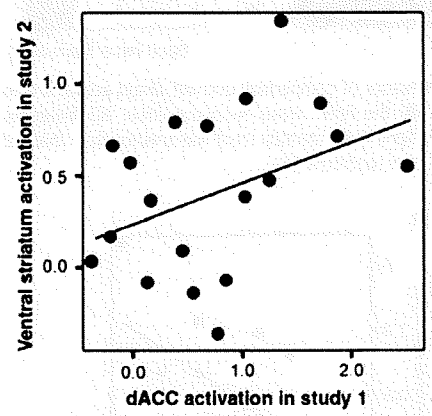

Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (–2, 10, 52). The y axis indicates the parameter estimates of the ventral striatum activation for MisSpHi-MisAvLo contrast at a peak voxel (–14, 2, –12). Positive correlation between dACC activation in study one and ventral striatum activation in study two across participants is shown ($r = 0.39$, $P = 0.01$).

When the comparison domain is not self-relevant, we do not feel strong envy, even if the possession is superior. When the comparison target is neither superior nor self-relevant, we are indifferent to the target. Activation of dACC was also modulated by possession quality and self-relevance. Stronger dACC activation was observed when one felt stronger envy. Moreover, between-participant correlation analysis demonstrated that people with stronger envy showed greater activation in dACC. At the behavioral level in study two, stronger schadenfreude was related to stronger envy, and schadenfreude arose when misfortune occurred to a person who was advantaged and self-relevant. Striatal activation was observed when misfortune happened to an envied person but not when it happened to a nonenvied person. Between-participant analysis revealed that people with stronger schadenfreude showed greater activation in the ventral striatum.

ACC activation in response to envy stimuli might reflect a painful feature of this emotion. It was comparable to caudal ACC activation in response to pain in the self but not to pain in others (empathic pain) (*12*), suggesting that the participants experienced a painful feeling. Activation in this region has been reported in response to social pain (distress of social exclusion) (*20*). Taken together, envy might be a social pain in the self, with feelings of being excluded from the field that one is concerned with.

We are usually motivated to maintain a positive self-concept (*16*), and we feel discomfort when our self-concept is threatened by others who outperform ourselves in a self-relevant domain. Considering the role of dACC in conflict-monitoring (*19*), the association between envy and dACC activation suggests that envy is a condition in which information recognized by social comparison conflicts with positive self-concept. Experiencing discomfort motivates us to reduce it. Discomfort arising from others outperforming us in our cherished domains can be resolved by reducing the relevance of the domain to us or changing relative performance (*16*). Students in our scenario might change their major or club at the university and, ultimately, their goals in life. Alternatively, they might make an effort to improve their own performance or possession. On the contrary, they might wish that the other lacks advantages, or they may even obstruct the advantaged student (with malice). Similarly, from an economic perspective, envy has productive and destructive effects on economic growth. It motivates the members in organizations to enhance their own performances or to sabotage their opponents' performances (*24*). When misfortune occurs to an advantaged person and contributes to narrowing the gap of relative performance in an important domain, discomfort or pain is reduced, and a pleasant feeling is induced. This pleasure at another's misfortune is correspondent to the activation of the ventral striatum and the medial orbitofrontal cortex (*25*, *26*). The striatum has also been implicated in altruistic punishment (*27*) and observing an unfair person receiving pain (*28*). Stronger dACC activation induced by the most envied student in study one predicted stronger ventral striatum activation when misfortunes occurred to the student in study two. This means that people who tend to have higher pain or conflict are more likely to have a strong pleasant feeling once they are relieved from this pain. Thus, our findings propose a neurocognitive mechanism of a psychologically rewarding reaction, schadenfreude, and its relation to envy. At the same time, ventral striatum activation without receiving an actual reward indicates that we did not evaluate objects solely by their absolute value but that social comparison plays a substantial role in evaluation (*29*).

References and Notes

1. B. Russell, *The Conquest of Happiness* (W.W. Norton, New York, 1930).
2. Aristotle, *The Art of Rhetoric* (Penguin Books, London, 1981).
3. W. G. Parrott, R. H. Smith, *J. Pers. Soc. Psychol.* **64**, 906 (1993).
4. R. H. Smith, W. G. Parrott, E. F. Diener, R. H. Hoyle, S. H. Kim, *Pers. Soc. Psychol. Bull.* **25**, 1007 (1999).
5. A. Tesser, *Adv. Exp. Soc. Psychol.* **21**, 181 (1988).
6. J. Rawls, *A Theory of Justice* (Harvard Univ. Press, Cambridge, MA, 1971).
7. R. Nozick, *Anarchy, State, and Utopia* (Basic Books, New York, 1974).
8. G. F. de la Mora, *Egalitarian Envy: The Political Foundations of Social Justice* (Paragon House, New York, 1987).
9. D. Hume, *A Treatise of Human Nature* (Oxford Univ. Press, Oxford, 1978).
10. L. Festinger, *Hum. Relat.* **7**, 117 (1954).
11. N. Eisenberg, *Novartis Found. Symp.* **278**, 71 (2007).
12. T. Singer *et al.*, *Science* **303**, 1157 (2004).
13. F. Heider, *The Psychology of Interpersonal Relations* (Wiley & Sons, New York, 1958).
14. B. de Spinoza, *The Ethics* (Biblio Bazaar, Charleston, SC, 2006).
15. W. W. van Dijk, J. W. Ouwerkerk, S. Goslinga, M. Nieweg, M. Gallucci, *Emotion* **6**, 156 (2006).
16. A. Tesser, D. Cornell, *J. Exp. Soc. Psychol.* **27**, 501 (1991).
17. D. M. Amodio *et al.*, *Psychol. Sci.* **15**, 88 (2004).
18. E. Harmon-Jones, *Biol. Psychol.* **67**, 51 (2004).
19. J. G. Kerns *et al.*, *Science* **303**, 1023 (2004).
20. N. I. Eisenberger, M. D. Lieberman, K. D. Williams, *Science* **302**, 290 (2003).
21. J. D. Greene, R. B. Sommerville, L. E. Nystrom, J. M. Darley, J. D. Cohen, *Science* **293**, 2105 (2001).
22. T. Sharot, A. M. Riccardi, C. M. Raio, E. A. Phelps, *Nature* **450**, 102 (2007).
23. Materials and methods are available as supporting material on *Science* Online.
24. E. Lazear, *J. Polit. Econ.* **97**, 561 (1989).
25. S. M. McClure, M. K. York, P. R. Montague, *Neuroscientist* **10**, 260 (2004).
26. E. Fehr, C. F. Camerer, *Trends Cogn. Sci.* **11**, 419 (2007).
27. D. J.-F. de Quervain *et al.*, *Science* **305**, 1254 (2004).
28. T. Singer *et al.*, *Nature* **439**, 466 (2006).
29. K. Fliessbach *et al.*, *Science* **318**, 1305 (2007).

30. We gratefully thank C. Frith for his valuable comments. This study was supported by a Health and Labor Sciences Research Grant for Comprehensive Research on Disability, Health, and Welfare (H20-SYOGAI-011) from the Japanese Ministry of Health, Labor, and Welfare, and a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H20-KOKORO-025) from the Japanese Ministry of Health, Labor, and Welfare. D.M. is support by MRC (UK).

Supporting Online Material

www.sciencemag.org/cgi/content/full/323/5916/937/DC1
Materials and Methods
SOM Text
Figs. S1 to S4
Table S1

8 September 2008; accepted 10 December 2008
10.1126/science.1165604

Schizophrenia Research 108 (2009) 78–84

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

Shoko Nozaki [a,b], Motoichiro Kato [b], Harumasa Takano [a,b], Hiroshi Ito [a], Hidehiko Takahashi [a], Ryosuke Arakawa [a], Masaki Okumura [a], Yota Fujimura [a], Ryohei Matsumoto [a], Miho Ota [a], Akihiro Takano [a], Akihiko Otsuka [d], Fumihiko Yasuno [a], Yoshiro Okubo [c], Haruo Kashima [b], Tetsuya Suhara [a,*]

[a] Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan
[b] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan
[c] Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan
[d] Otsuka Clinic, Chiba, Japan

ARTICLE INFO

Article history:
Received 3 July 2008
Received in revised form 14 October 2008
Accepted 8 November 2008
Available online 4 December 2008

Keywords:
Schizophrenia
Dopamine synthesis
[^{11}C]DOPA
Positron emission tomography (PET)
PANSS

ABSTRACT

The dopamine hypothesis has been the most widely known theory concerning schizophrenia. However, the exact mechanism including presynaptic dopaminergic activity and its relationship with symptom severity still remains to be revealed. We measured presynaptic dopamine synthesis using positron emission tomography (PET) with L-[β-^{11}C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as k_i values, were obtained using a graphical method, and the occipital cortex was used as reference region. Regions of interest were placed on the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). We found significantly higher k_i values in patients than in controls in the left caudate nucleus, but not in the other regions. The k_i values in the thalamus exhibited a significant positive correlation with the PANSS total scores. Furthermore, a significant positive correlation was observed between the PANSS positive subscale scores and k_i values in the right temporal cortex. Patients with schizophrenia showed higher dopamine synthesis in the left caudate nucleus, and dopaminergic transmission in the thalamus and right temporal cortex might be implicated in the expression of symptoms in schizophrenia.

1. Introduction

Positron emission tomography (PET) has allowed us to investigate the dopamine hypothesis in living human brain. Since there is no ideal animal model of schizophrenia, PET investigation is still the most useful method for investigating neurotransmission in patients. As for postsynaptic dopaminergic receptors, several studies have investigated striatal (Farde et al., 1990; Nordström et al., 1995; Wong et al., 1986) and extrastriatal (Suhara et al., 2002; Yasuno et al., 2004) D_2 receptor (D_2R) binding by the use of PET. Although studies investigating D_2R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D_2R binding have repeatedly reported its reduction in the anterior cingulate cortex (Suhara et al., 2002) and the thalamus in schizophrenia (Talvik et al., 2003; Yasuno et al., 2004). Regarding intrasynaptic function, striatal dopamine release was reported to be enhanced in schizophrenia (Breier et al., 1997; Laruelle et al., 1996). On the other hand, many studies did not find any change in dopamine transporter binding in the striatum of schizophrenia (Laakso et al., 2000;

* Corresponding author. Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. Tel.: +81 43 206 3194; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

0920-9964/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2008.11.006

Laruelle et al., 2000; Schmitt et al., 2005; Yang et al., 2004). These findings suggest that patients with schizophrenia may have elevated presynaptic dopamine synthesis, and investigations on presynaptic dopaminergic function in extrastriatal regions might be critical for providing an understanding of the pathophysiology of schizophrenia.

Radiolabeled L-DOPA, a precursor of dopamine, has been used to investigate presynaptic dopamine synthesis. L-DOPA is transported through the blood–brain barrier (BBB), taken up by presynaptic monoaminergic neurons, and metabolized to dopamine by aromatic amino acid decarboxylase (AADC). Previous studies on the dopamine synthesis of schizophrenia used 6-[^{18}F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashef et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[β-^{11}C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[^{18}F]fluoro-L-DOPA, which is widely used in schizophrenia research, indicated elevated dopamine synthesis (Hietala et al., 1995, 1999; Lindström et al., 1999; McGowan et al., 2004; Reith et al., 1994), elevated dopamine turnover (Kumakura et al., 2007), only higher variability (Dao-Castellana et al., 1997), and even reduced synthesis (Elkashef et al., 2000) in the striatum.

The 3-O-methyl metabolite of L-DOPA crossing the BBB can reportedly cause an error in quantification of the dopamine synthesis rate (Dhawan et al., 1996; Melega et al., 1990; Wahl et al., 1994). However, 3-O-methylation of L-[β-^{11}C]DOPA does not take place readily and rapidly when compared with 6-[^{18}F]fluoro-L-DOPA (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Recently, we evaluated the accuracy of quantitative analyses of L-[β-^{11}C]DOPA PET studies (Ito et al., 2006). In the current study, we investigated regional dopamine synthesis and its relationship with the severity of positive and negative symptoms in patients with schizophrenia using L-[β-^{11}C]DOPA.

2. Methods

2.1. Participants

Fourteen (8 males and 6 females) drug-naïve and 4 (2 males and 2 females) 3-month drug-free patients (35.6±7.4 years, mean±SD) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia or schizophreniform disorder were recruited from the outpatient units of university hospitals, their affiliated psychiatric hospitals, and a mental clinic. On the day of the PET study, the diagnosis was re-evaluated by 3 experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The severity of psychotic symptoms was also evaluated by the same 3 psychiatrists with the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Igarashi et al., 1998). Each interview was conducted by 2 of 3 authors (S.N., F.Y., M.O.) and one other psychiatrist. Patients with schizophreniform disorder (2 males and 2 females) at the time of the PET study were followed up for at least 6 months from onset, confirming that they eventually met the criteria of schizophrenia. Twenty (10 males and 10 females) healthy volunteers (35.1±9.5 years) were recruited as controls through public notices. All the subjects were examined by physicians to obtain data concerning their educational background as well as current and past medical problems, and family history by unstructured interview and a general questionnaire. Handedness was assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971). The control subjects were matched with the patients for age, gender, education, and handedness. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. The demographic characteristics of all participants are shown in Table 1. Exclusion criteria of patients and controls were as follows: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse including alcohol; (3) previous episodes of mood disorder. One patient was excluded because of a large cyst in the cerebellum (data not shown).

After giving explanation of the study, written informed consent was obtained from all patients and control subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET study

All the participants were instructed to fast for 4 h before PET scan in order to avoid the influence of the plasma concentration of neutral amino acid (NAA) on the L-[β-^{11}C]DOPA uptake rate. A PET scanner (ECAT EXACT HR, CTI-Siemens, Knoxville, TN), providing 63 planes with an axial field of view of 15.5-cm, was used. A head fixation device (Fixster, Stockholm Sweden) was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Data acquisition was performed in 3-dimensional mode with the interplane septa retracted. A bolus of 331.5 to 401.8 MBq (373.0±14.1 MBq, mean±SD) of L-[β-^{11}C]DOPA with specific radioactivities (9.9–156.4 GBq/μmol) was injected intravenously via the antecubital vein and flushed rapidly with 20 mL of saline. Dynamic scans were performed for 64 min immediately after the injection. The scanning sequence consisted of seven 1-min frames, five 2-min frames, four 3-min frames, and seven 5-min frames. All emission scan data were reconstructed with a Hanning filter with a cutoff frequency of 0.4 (final in-plane resolution: 7.5 mm full width at half maximum).

Table 1
Demographic and clinical characteristics of patients with schizophrenia and normal controls

	Controls (n=20)	Patients (n=18)
Gender, M/F	10/10	10/8
Age, y, mean±SD	35.1±9.5	35.6±7.4
Range	20–55	20–52
Medication, no. naïve (M/F)/free (M/F)		14 (8/6)/4 (2/2)
Handedness, no. right/left	20/0	18/0
Education, y, mean (range)	15.1 (12–9)	14.1 (9–16)
No. of smokers (M/F)	4 (4/0)	6 (4/2)
Duration of illness, mo, mean (range)		26.4 (1–120)
PANSS		
Whole score		
Mean±SD		79.2±21.4
Range		46–124
Subscales		
Positive (mean±SD)		22.6±7.3
Negative (mean±SD)		17.1±6.5
General psycho (mean±SD)		39.6±11.0

Table 2
k_i values of each ROI in patients with schizophrenia and normal controls

Region	L/R	Controls	Patients	ANCOVA#	
		(n=20)	(n=18)	F	p
Parahippocampus	L	4.54±1.13	4.91±1.45	0.704	0.407
	R	4.76±1.11	4.47±1.29	0.528	0.472
Temporal cortex	L	1.92±0.99	1.98±0.81	0.041	0.842
	R	1.86±0.83	1.92±0.87	0.037	0.849
Prefrontal cortex	L	1.31±0.73	1.22±0.64	0.324	0.573
	R	1.35±0.73	1.35±0.57	0	1.000
Thalamus	L	3.55±1.60	3.19±1.72	0.549	0.463
	R	3.11±1.45	3.09±1.54	0.001	0.970
Putamen	L	15.52±2.04	15.76±2.14	0.139	0.711
	R	15.39±2.31	14.90±3.01	0.329	0.570
Caudate	L	12.89±2.68	14.66±2.38	4.409	0.043*
	R	13.71±2.74	13.59±2.09	0.026	0.872
Anterior cingulate	L	2.74±1.33	3.05±1.50	0.445	0.509
	R	3.24±1.73	3.00±1.13	0.288	0.595

Dopamine synthesis rates, expressed as $k_i \times 1000$, were presented as mean± standard deviation.
#: Analysis of covariance with age as covariate (df=1, 35).
L indicates left and R indicates right. The symbol * represents $p<0.05$.

2.3. Magnetic resonance images

For each participant, a structure magnetic resonance (MR) image was obtained. All MR imaging studies were performed with a 1.5-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, TE: 9.2 ms; repetition time, TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256×256; slice thickness: 1 mm).

2.4. Data analysis

All MR images were coregistered to the PET summation images of all frames using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROIs) were drawn on the coregistered MR images, referring to the human brain atlas (Mai et al., 1997), and then transferred to the PET images. ROIs were defined for the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. The ROIs were set on both left and right sides of the brain and those values were independently evaluated. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

The overall uptake rate constant k_i of L-[β-^{11}C]DOPA, which indicates the net dopamine synthesis rate, was determined for each ROI by the graphical plot analysis method developed by Gjedde and Patlak (Gjedde, 1982; Ito et al., 2006; Patlak and Blasberg, 1985). k_i values can be estimated by simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F_{t>t^*}$$

where C_i is the total radioactivity concentration in a brain region that can be measured by PET, C_i' is the total radioactivity concentration in the reference brain region with no irreversible compartments, and t^* is the equilibrium time of the compartment for unchanged radioligand in the brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after the time t^*, yields a straight line with the slope k_i and intercept F. In the present study, the occipital cortex was used as reference region (Ito et al., 2006). A range of equilibrium time t^* of 31.5 to 61.5 min was used.

ROI analyses were independently performed by 3 researchers who were blinded to the diagnoses. The intraclass correlation coefficient across all ROIs was 0.976 (McGraw and Wong, 1996), considered as excellent. In order to reduce variance, the k_i values by one researcher that most frequently showed medium values among those obtained by the 3 researchers were used for the following analyses.

2.5. Statistical analysis

Demographic variables were compared by independent sample t-test or chi-square test. Differences in the k_i values for each of the 7 × 2 brain regions between patients and controls were evaluated by one-way univariate analyses of covariance with age as a covariate, since an effect of age on k_i values has been reported (Ota et al., 2006). Pearson's correlation coefficients were calculated between the PANSS scores and k_i values. A significance level of $p<0.05$ (two-tailed) was used both in the comparison analyses between groups and in the correlation analyses.

3. Results

3.1. Demographic data

The demographic data of schizophrenia patients and controls are shown in Table 1. There were no significant differences between patients and controls in terms of age, gender, education, handedness, and the injected dose and

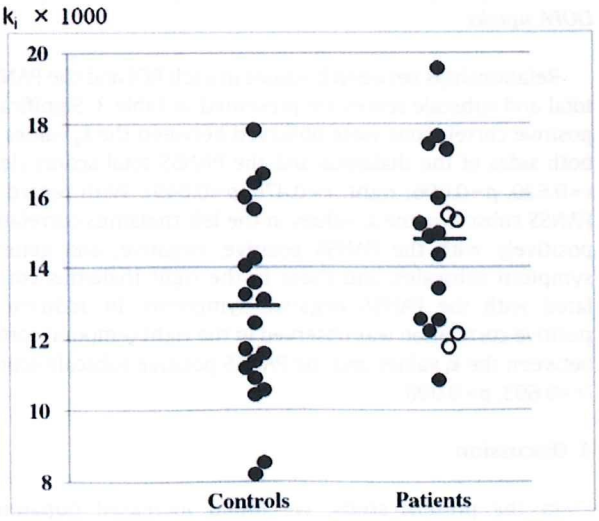

Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those of drug-free patients.

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

Region	L/R	Total scores		Positive symptoms		Negative symptoms		General symptoms	
		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.

Journal of Psychiatric Research 43 (2009) 1219–1223

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Increase in thalamic binding of [^{11}C]PE2I in patients with schizophrenia: A positron emission tomography study of dopamine transporter

Ryosuke Arakawa [a,b], Tetsuya Ichimiya [a,b], Hiroshi Ito [a], Akihiro Takano [a], Masaki Okumura [a,b], Hidehiko Takahashi [a], Harumasa Takano [a], Fumihiko Yasuno [a], Motoichiro Kato [c], Yoshiro Okubo [b], Tetsuya Suhara [a,*]

[a] Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263-8555, Japan
[b] Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan
[c] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 15 January 2009
Received in revised form 5 March 2009
Accepted 21 April 2009

Keywords:
Dopamine transporter
Schizophrenia
Thalamus
Positron emission tomography
[^{11}C]PE2I
PANSS

ABSTRACT

Previous *in vivo* imaging studies reported no difference in dopamine transporter (DAT) bindings in the striatum between control subjects and patients with schizophrenia. However, as the signals of radioligands with moderate affinity were insufficient for allowing the evaluation of small amounts of DAT, DAT binding in extrastriatal regions has not been determined. Positron emission tomography scanning using [^{11}C]PE2I was performed on eight patients with schizophrenia and twelve normal control subjects. Binding potential (BP_{ND}) for DAT in the caudate, putamen, thalamus and substantia nigra was calculated, using the cerebellum as reference region. In patients with schizophrenia, clinical symptoms were evaluated by Positive and Negative Syndrome Scale (PANSS). BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than in control subjects ($P = 0.044$). In patients with schizophrenia, there were significantly positive correlations between BP_{ND} in the thalamus and total ($r = 0.75$), positive ($r = 0.78$) and negative PANSS scores ($r = 0.82$). Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

1. Introduction

One of the most accepted hypotheses concerning the pathophysiology of schizophrenia are the hyperactivity of dopaminergic neurotransmission. This 'dopamine hypothesis' is supported by the facts that antipsychotic effects are mainly related to dopamine D_2 receptor antagonism and that dopamine stimulating agents can cause psychotic symptoms such as hallucination or delusion. Dopamine transporter (DAT) plays a role in the reuptake of dopamine into pre-synaptic nerves and regulates dopaminergic transmission in the synaptic cleft. DAT inhibitors such as cocaine increase dopamine concentration in the synaptic cleft (Schlaepfer et al., 1997) and worsen the clinical course of schizophrenia, e.g., exacerbating positive and negative symptoms, increasing the risk of relapse, or hospitalization (Green, 2005).

Previous *in vivo* imaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) reported no difference in DAT bindings between control subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004) except for one study reporting lower binding in patients with schizophrenia as compared with controls (Mateos et al., 2007). However, those studies evaluated DAT binding only in the striatum, as DAT density in extrastriatal regions is very low (in a postmortem human study, [^{125}I]PE2I binding in the thalamus was reported to be 15% of that in the striatum and negligible in the cortex) (Hall et al., 1999). The recent development of [^{11}C]PE2I, which has high affinity ($K_i = 17$ nM) and selectivity (more than 30-fold for other monoamine transporters) for DAT, allows the evaluation of extrastiatal DAT bindings (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, we evaluated DAT binding in the striatal and extrastriatal regions of patients with schizophrenia using [^{11}C]PE2I.

2. Materials and methods

2.1. Subjects

Eight patients (age range 25–52 yr, mean ± SD: 36.5 ± 9.5 yr) diagnosed with schizophrenia or schizophreniform disorder according to DSM-IV criteria participated in this study. Four patients with schizophreniform disorder met the criteria for schizophrenia at six month follow-up. Exclusion criteria were current

* Corresponding author. Tel.: +81 43 206 3251; fax: +81 43 253 0396.
E-mail address: suhara@nirs.go.jp (T. Suhara).

0022-3956/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2009.04.009

Table 1
Demographic and clinical characteristics.

	Controls	Patients
N	12	8
Age (years)	33.2 ± 12.0	36.5 ± 9.5
Gender (M/F)	10/2	6/2
Naïve/free		6/2
Duration of illness (months)		32.1 ± 42.8
PANSS (total)		77.8 ± 18.8
Positive		17.8 ± 4.8
Negative		18.9 ± 6.5
General		41.1 ± 10.8

Values are mean ± SD.

or past substance abuse, organic brain disease, or epilepsy. Demographic and clinical data are shown in Table 1. Six of the patients were antipsychotic naïve and two had been antipsychotic-free for at least six months before the PET scan. Three patients had taken benzodiazepines the night before the PET scan.

Psychopathological symptoms were assessed by three experienced psychiatrists on the same day as the PET scans using the Positive and Negative Syndrome Scale (PANSS), and consensus ratings were used. PANSS scores used were total score and subscores for positive symptom, negative symptom and general symptom.

Twelve normal control subjects (age range 23–56 yr, mean ± SD: 33.2 ± 12.0 yr) also participated. None of them had a history of psychiatric or neurological disorders, brain injury, chronic somatic illness, or substance abuse. None had taken any drugs within two weeks before the PET scan.

After complete description of this study, written informed consent was obtained from all subjects. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Data were collected from 4/2003 to 8/2006.

2.2. PET procedure

A PET scanner system, ECAT EXACT HR+(CTI-Siemens, Knoxville, TN, USA), was used for all measurements. A head fixation device was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source before each scan. A dynamic PET scan was performed for 90 min (20 s × 9, 1 min × 5, 2 min × 4, 4 min × 11, 5 min × 6) after intravenous bolus injection of 214.7 ± 13.7 MBq (mean ± SD) of [^{11}C]PE2I. The specific radioactivity of [^{11}C]PE2I was 344.5 ± 355.3 MBq/nmol. Injected dose and specific radioactivity between the control and patient groups were not significantly different (two-tailed *t*-test; $P = 0.15$ and $P = 0.16$, respectively). Since two previous quantitative studies of [^{11}C]PE2I had reported good reliability with scan times of 63 and 69 min, the scan time of 90 min was considered sufficient for estimation of DAT bindings especially in extrastriatal regions (Hirvonen et al., 2008; Jucaite et al., 2006). Magnetic resonance (MR) images of the brain were acquired with a 1.5 Tesla MR imaging system, Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images were obtained at 1 mm slices. All subjects were free of organic brain lesions.

2.3. Data analysis

All MR images were coregistered to the PET images using the statistical parametric mapping (SPM2) system. MR images were transformed into the standard brain size and shape by SPM2 (anatomic standardization). All PET images were also transformed into the standard brain size and shape using the same parameters as the MR image standardization. Thus, brain images of all subjects had the same anatomic format (Ito et al., 2008). Motion corrections were not made.

Regions of interest (ROIs) were drawn on all anatomically standardized PET images with reference to the T1-weighted MR images. ROIs were defined for the cerebellar cortex, caudate head, putamen, substantia nigra and thalamus (Fig. 1).

Binding potential (BP_{ND}) was calculated by the simplified reference tissue model (SRTM) method. The cerebellum was used as reference region because of its negligible density of DAT (Hall et al., 1999). In this study, the software package PMOD (PMOD Technologies, Zurich, Switzerland) was used to calculate BP_{ND}.

2.4. Statistics

Statistical analysis concerning the difference of BP_{ND} for each ROI between patients and controls was performed by two-tailed *t*-test. Correlations between BP_{ND} of patients with schizophrenia and age, duration of illness, and PANSS scores were evaluated using Pearson's correlation coefficient. In all analyses, $P < 0.05$ was considered significant.

3. Results

The BP_{ND} values of control subjects and patients with schizophrenia are shown in Table 2. The BP_{ND} value in the thalamus was significant higher in patients with schizophrenia than in con-

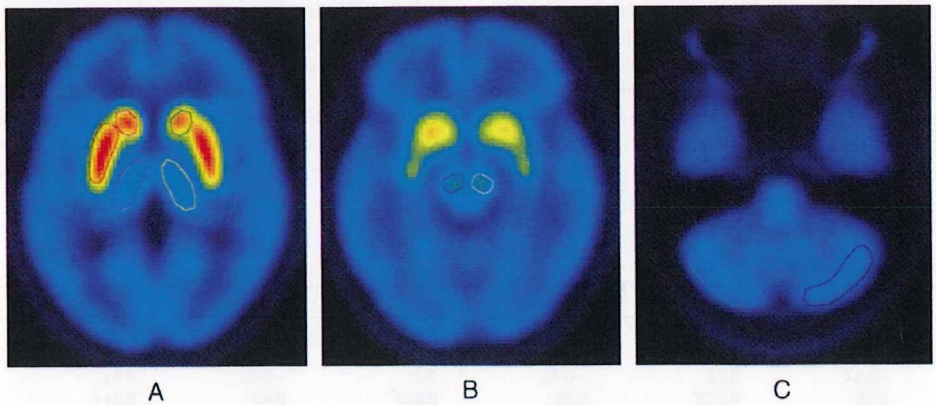

Fig. 1. Summated images of [^{11}C]PE2I with regions of interest. Average normalized images of twelve control subjects are shown at the level of caudate, putamen and thalamus (A), substantia nigra (B) and cerebellum (C).

Table 2
BP_{ND} in all regions.

	BP_{ND}[a]				*t*-test	
Region	Controls	Patients	% Change[b]	Effect size	*t*	*P*
Caudate	7.54 ± 1.22	8.21 ± 1.38	8.9 ± 18.4 (−6.5–24.2)%	0.55	1.14	0.27
Putamen	7.54 ± 1.25	8.23 ± 0.71	9.2 ± 9.4 (1.3–17.0)%	0.55	1.41	0.18
Thalamus	0.28 ± 0.08	0.36 ± 0.07	27.9 ± 25.8 (6.3–49.5)%	1.0	2.16	0.044*
Substantia nigra	1.09 ± 0.16	1.13 ± 0.12	4.1 ± 11.3 (−5.3–13.6)%	0.25	0.66	0.52

[a] Values are mean ± SD.
[b] Values are mean ± SD and 95% confidence interval.
* $P < 0.05$.

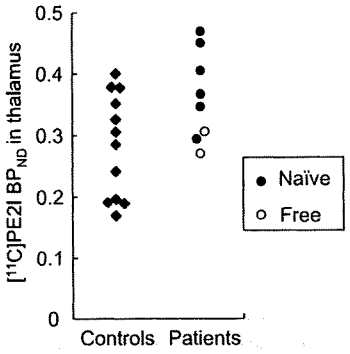

Fig. 2. BP_{ND} in the thalamus of normal controls and patients with schizophrenia. BP_{ND} of patients with schizophrenia was significantly higher than that of the control group (df = 18, $t = 2.16$, $P = 0.044$).

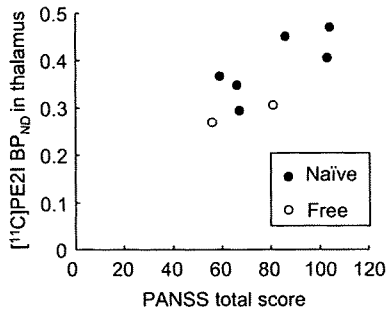

Fig. 3. Relationship between BP_{ND} in the thalamus of patients with schizophrenia and total PANSS score. There were significantly positive correlations between BP_{ND} and total PANSS score ($r = 0.75$, $P = 0.032$).

trols (df = 18, $t = 2.16$, $P = 0.044$) (Table 2, Fig. 2). There were no significant differences in BP_{ND} between the two groups in the caudate, putamen or substantia nigra. In patients with schizophrenia, there were significant positive correlations between BP_{ND} in the thalamus and total PANSS score ($r = 0.75$, $P = 0.032$), positive ($r = 0.78$, $P = 0.023$) and negative PANSS scores ($r = 0.82$, $P = 0.014$), but no correlation was observed with the general PANSS score (Table 3, Fig. 3). There was no significant correlation between BP_{ND} in other regions and clinical symptoms. There was also no significant correlation between BP_{ND} in each region and age or duration of illness.

4. Discussion

The *in vivo* evaluation of thalamic DAT had not been previously performed in detail due to its very low density as compared to that in the striatum (Hall et al., 1999). [^{11}C]PE2I allows the estimation of specific binding in low density regions because of its high affinity and selectivity for DAT (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than that of control subjects and was positively correlated with clinical symptoms. There was no significant difference in the area under the time activity curves of the cerebellum between controls and the patient group (two-tailed *t*-test; $P = 0.37$), suggesting that the higher DAT bindings were not due to cerebellar difference. An effect of endogenous dopamine on [^{11}C]PE2I binding has not been reported. However, as [^{11}C]PE2I is a high-affinity radioligand ($K_i = 17$ nM), it is reasonable to expect such an effect based on the result from a high-affinity ralioligand for serotonin transporter, [^{11}C]DASB ($K_i = 1.1$ nM) (Wilson et al., 2000). [^{11}C]DASB binding did not change by manipulation of endogenous serotonin in human brain (Praschak-Rieder et al., 2005; Talbot et al., 2005). Although these results may not apply directly to [^{11}C]PE2I binding, high [^{11}C]PE2I binding can nevertheless be interpreted as high DAT density.

The thalamus has been considered as the key brain structure of processing or integrating sensory information related to emotional or cognitive functions (Clinton and Meador-Woodruff, 2004). Several studies have reported morphological abnormalities of the thalamus in patients with schizophrenia using MR imaging or postmortem studies (Clinton and Meador-Woodruff, 2004). Regarding dopaminergic transmission, increased dopamine concentrations in the thalamus of patients with schizophrenia were reported in a postmortem study (Oke and Adams, 1987). The distribution of dopaminergic innervation in the thalamus was reported recently using immunohistochemistry in monkey (Melchitzky and Lewis, 2001) and human brain (Garcia-Cabezas et al., 2007). These studies reported that thalamic dopamine or DAT was relatively higher in the midline and mediodorsal nuclei. In patients

Table 3
Correlation between regional BP_{ND} and PANSS scores.

	Total		Positive		Negative		General	
Region	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Caudate	−0.04	0.93	0.03	0.95	0.10	0.81	−0.14	0.74
Putamen	−0.44	0.28	−0.42	0.31	−0.03	0.93	−0.55	0.15
Thalamus	0.75	0.032*	0.78	0.023*	0.82	0.014*	0.47	0.24
Substantia nigra	0.04	0.93	0.26	0.53	0.03	0.94	−0.07	0.86

* $P < 0.05$.

with schizophrenia, lower dopamine D_2 receptor binding was observed in the thalamus using PET with [^{11}C]FLB457 (Buchsbaum et al., 2006; Talvik et al., 2003; Yasuno et al., 2004) and [^{11}C]raclopride (Talvik et al., 2006). Significant differences in calcyon and spinophilin, dopamine receptor-associated intracellular proteins, and no difference in vesicular monoamine transporter (VMAT) binding of the thalamus were reported in a postmortem study of patients with schizophrenia and controls (Clinton et al., 2005). Assuming that low dopamine D_2 receptor binding is related to the disruption of the feedback system of dopamine release mediated by GABA interneuron (Takahashi et al., 2006), a high turnover of dopamine at the synapse would exist as a hyper-dopaminergic state. Although the function of DAT in the thalamus has remained unclear, high DAT bindings may suggest a hyper-dopaminergic state of pre-synaptic dopamine function in patients with schizophrenia.

Most of the previous PET and SPECT studies reported that DAT binding in the striatum did not differ between subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004), and our present results were in line with these reports. DAT binding in the substantia nigra also showed no difference between control subjects and patients with schizophrenia. However, BP_{ND} in the striatum using SRTM can be underestimated as compared to the values by kinetic model analyses with arterial blood sampling (Hirvonen et al., 2008; Jucaite et al., 2006). This might affect the results in the striatum.

In this study, the number of subjects was small, and in the statistical analysis we did not perform multiple comparisons regarding group differences of BP_{ND} between patients and controls to avoid type II error. Moreover, two of the eight patients were in a drug-free state, not drug-naïve state. Nonetheless, even when the two drug-free patients were excluded, the group difference of BP_{ND} in the thalamus was still observed (two-tailed t-test; $P = 0.018$). Further study with larger numbers of subjects in a drug-naïve state will be needed.

In conclusion, [^{11}C]PE2I binding in the thalamus of patients with schizophrenia was significantly higher than in control subjects and was correlated with clinical symptoms. Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

Conflict of interest

All authors have no conflicts of interest.

Contributors

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

Role of funding source

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. The sponsors of the study had no role in the study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Acknowledgements

We thank Mr. Katsuyuki Tanimoto, Mr. Takahiro Shiraishi, Mr. Akira Ando and Mr. Toshio Miyamoto for their assistance in performing the PET experiments, and Ms. Yoshiko Fukushima for her help as clinical research coordinator at the National Institute of Radiological Sciences.

References

Buchsbaum MS, Christian BT, Lehrer DS, Narayanan TK, Shi B, Mantil J, et al. D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. Schizophrenia Research 2006;85:232–44.

Clinton SM, Meador-Woodruff JH. Thalamic dysfunction in schizophrenia: neurochemical, neuropathological, and in vivo imaging abnormalities. Schizophrenia Research 2004;69:237–53.

Clinton SM, Ibrahim HM, Frey KA, Davis KL, Haroutunian V, Meador-Woodruff JH. Dopaminergic abnormalities in select thalamic nuclei in schizophrenia: involvement of the intracellular signal integrating proteins calcyon and spinophilin. The American Journal of Psychiatry 2005;162:1859–71.

Garcia-Cabezas MA, Rico B, Sanchez-Gonzalez MA, Cavada C. Distribution of the dopamine innervation in the macaque and human thalamus. NeuroImage 2007;34:965–84.

Green AI. Schizophrenia and comorbid substance use disorder: effects of antipsychotics. The Journal of Clinical Psychiatry 2005;66(Suppl. 6):21–6.

Hall H, Halldin C, Guilloteau D, Chalon S, Emond P, Besnard J, et al. Visualization of the dopamine transporter in the human brain postmortem with the new selective ligand [125I]PE2I. NeuroImage 1999;9:108–16.

Halldin C, Erixon-Lindroth N, Pauli S, Chou YH, Okubo Y, Karlsson P, et al. [11C]PE2I: a highly selective radioligand for PET examination of the dopamine transporter in monkey and human brain. European Journal of Nuclear Medicine and Molecular Imaging 2003;30:1220–30.

Hirvonen J, Johansson J, Teras M, Oikonen V, Lumme V, Virsu P, et al. Measurement of striatal and extrastriatal dopamine transporter binding with high-resolution PET and [11C]PE2I: quantitative modeling and test-retest reproducibility. Journal of Cerebral Blood Flow and Metabolism 2008;28:1059–69.

Hsiao MC, Lin KJ, Liu CY, Tzen KY, Yen TC. Dopamine transporter change in drug-naive schizophrenia: an imaging study with 99mTc-TRODAT-1. Schizophrenia Research 2003;65:39–46.

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;39:555–65.

Jucaite A, Odano I, Olsson H, Pauli S, Halldin C, Farde L. Quantitative analyses of regional [11C]PE2I binding to the dopamine transporter in the human brain: a PET study. European Journal of Nuclear Medicine and Molecular Imaging 2006;33:657–68.

Laakso A, Vilkman H, Alakare B, Haaparanta M, Bergman J, Solin O, et al. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. The American Journal of Psychiatry 2000;157:269–71.

Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, et al. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [123I]beta-CIT. Biological Psychiatry 2000;47:371–9.

Lavalaye J, Linszen DH, Booij J, Dingemans PM, Reneman L, Habraken JB, et al. Dopamine transporter density in young patients with schizophrenia assessed with [123]FP-CIT SPECT. Schizophrenia Research 2001;47:59–67.

Mateos JJ, Lomena F, Parellada E, Mireia F, Fernandez-Egea E, Pavia J, et al. Lower striatal dopamine transporter binding in neuroleptic-naive schizophrenic patients is not related to antipsychotic treatment but it suggests an illness trait. Psychopharmacology 2007;191:805–11.

Melchitzky DS, Lewis DA. Dopamine transporter-immunoreactive axons in the mediodorsal thalamic nucleus of the macaque monkey. Neuroscience 2001;103:1033–42.

Oke AF, Adams RN. Elevated thalamic dopamine: possible link to sensory dysfunctions in schizophrenia. Schizophrenia Bulletin 1987;13:589–604.

Praschak-Rieder N, Wilson AA, Hussey D, Carella A, Wei C, Ginovart N, et al. Effects of tryptophan depletion on the serotonin transporter in healthy humans. Biological Psychiatry 2005;58:825–30.

Schlaepfer TE, Pearlson GD, Wong DF, Marenco S, Dannals RF. PET study of competition between intravenous cocaine and [11C]raclopride at dopamine receptors in human subjects. The American Journal of Psychiatry 1997;154:1209–13.

Schmitt GJ, Meisenzahl EM, Frodl T, La Fougere C, Hahn K, Moller HJ, et al. The striatal dopamine transporter in first-episode, drug-naive schizophrenic patients: evaluation by the new SPECT-ligand[99mTc]TRODAT-1. Journal of Psychopharmacology 2005;19:488–93.