

## I-123 iomazenil SPECT in patients with mental disorders

Yoshiaki NAKABEPPU,\* Masayuki NAKAJO,\* Tetsuro NARUO,\*\* Yoshihiko OBO,\*\*\*  
Shinichi NOZOE,\*\*\*\* Morikuni TAKIGAWA,\*\*\* Shinsaku TSUCHIMUCHI,\*  
Atsushi TANI\* and Hiromitsu TANAKA\*\*

*Departments of \*Radiology, \*\*First Internal Medicine, \*\*\*Psychiatry and \*\*\*\*Psychosomatic Medicine,  
Faculty of Medicine, Kagoshima University*

The purpose of this study is visual evaluation of the distribution of I-123 iomazenil in the brains of patients with various types of mental disorder and to examine whether chronic administration of a clinical dose of benzodiazepine (BZ) affects the binding of I-123 iomazenil to BZ receptors (BZR). The subjects were 10 patients with mental disorders (3 males and 7 females) with a mean age of 26.8 yrs (range 19–39 yrs). Four of 10 patients were administered BZ for over 3 months and the other six were free of BZ for over one month. The SPECT images were obtained at 5–25 min (early) and 170–190 min (delayed), after the bolus i.v. injection of 167 MBq of I-123 iomazenil, with a triple-head gamma camera. The images were visually evaluated and the washout ratios of each region were calculated. In visual analysis, abnormalities were recognized in 5 patients on the delayed SPECT. The abnormalities were recognized more frequently in the superior frontal lobe. The washout ratio was higher in the BZ (+) patient group than in the BZ (–) patient group. I-123 iomazenil is useful, because the SPECT image with I-123 iomazenil reflects the distribution of BZR on the brain and provides the different information from that obtained with perfusion SPECT, X-ray CT or MRI. The rapid washout of I-123 iomazenil from the brains of BZ (+) patients suggests that chronic administration of a clinical dose of BZ affects the binding of I-123 iomazenil to BZR.

**Key words:** I-123 iomazenil, mental disorder, washout ratio, SPECT

### INTRODUCTION

IOMAZENIL is an iodine-containing analog of the benzodiazepine (BZ) receptor antagonist flumazenil.<sup>1</sup> The I-123 labeled compound (I-123 iomazenil) has been used to image the BZ receptor distribution in human and non-human primate brains with SPECT.<sup>1–3</sup> The distribution of I-123 iomazenil has been reported in patients with such mental disorders as anxiety disorder<sup>4,5</sup> and panic disorder.<sup>6,7</sup> We studied the scintigraphy with I-123 iomazenil in 10 patients with 6 types of mental disorders (obsessive-compulsive disorder, somatization disorder, bulimia nervosa, panic disorder, dissociative amnesia and generalized anxiety disorder). This paper reports the visual and semiquantitative evaluation of the distribution of I-123

iomazenil in the patients with 6 types of mental disorder.

### MATERIALS AND METHODS

#### *I-123 iomazenil*

I-123 iomazenil was obtained from Nihon Medi-Physics Co., Ltd. (Hyogo, Japan). It was prepared at a specific concentration of 111 MBq/ml with radiochemical purity of over 95%. Each vial contained 167 MBq of I-123 and 0.75 µg of iomazenil.

#### *Patients* (Table 1)

We studied 10 (3 males and 7 females) patients with a mean age of 26.8 yrs (range 19–39 yrs), who were diagnosed according to the ICD-10 criteria as having obsessive-compulsive disorder (OD) in 4, somatization disorder (SD) in 2, bulimia nervosa (BN), panic disorder (PD), dissociative amnesia (DA) and generalized anxiety disorder (gAD) in one each. Before this study, we had obtained permission for the clinical use of I-123 iomazenil

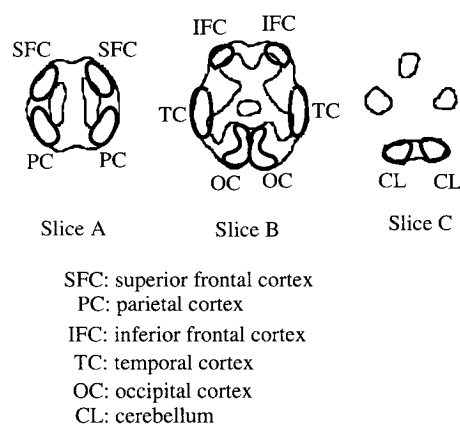
Received February 24, 1997, revision accepted July 4, 1997.

For reprint contact: Yoshiaki Nakabeppu, M.D., Faculty of Medicine, Kagoshima University, 8–35–1 Sakuragaoka, Kagoshima 890, JAPAN.

**Table 1** Patients and with mental disorder clinical data

Patient no.	Age (yr)	Sex	Disease (The ICD-10 classification)*	Benzodiazepine	CT	MRI	Perfusion SPECT
1	33	Female	Obsessive-compulsive disorder (F42.2)	Free over 3 m	(-)	(-)	W.N.L.
2	30	Female	Same as above	Free over 1 m	(-)	(-)	(-)
3	23	Female	Same as above	Free	(-)	W.N.L.	(-)
4	22	Female	Same as above	Bromazepam 6 mg/day	W.N.L.	(-)	W.N.L.
5	29	Male	Somatization disorder (F45.0)	Free	(-)	(-)	(-)
6	31	Female	Same as above	Free	(-)	(-)	(-)
7	22	Female	Bulimia nervosa (F50.2)	Free	(-)	(-)	W.N.L.
8	19	Male	Dissociative amnesia (F44.0)	Bromazepam 4 mg/day	W.N.L.	W.N.L.	(-)
9	20	Male	Panic disorder (F41.0)	Alprazolam 0.8 mg/day	(-)	W.N.L.	(-)
10	39	Female	Generalized anxiety disorder (F41.1)	Alprazolam 1.2 mg/day	(-)	W.N.L.	(-)

\* The ICD-10 classification of mental and behavioral disorder



**Fig. 1** The location of the ROIs on the brain SPECT images for a washout rate study of I-123 iomazenil.

from the committee on drug diagnosis and therapeutic study in Kagoshima University Hospital, and all patients gave informed consent. Four of the 10 patients were administered BZ for over 3 months and the other six were free of BZ for over one month. None of the patients had a neurological abnormality. X-ray CT, MRI and/or brain perfusion SPECT had been performed in 7 patients, and there was no abnormality in the findings obtained by these methods.

#### SPECT study

Three hundred mg of potassium iodide per day was orally given to each patient from one day before to one day after the study to protect the thyroid gland from the uptake of free I-123. I-123 iomazenil (167 MBq) was intravenously injected as a bolus within a few seconds. The SPECT data were acquired twice at 5–25 min and 170–190 min, after i.v. injection of I-123 iomazenil, with a triple-head rotating gamma camera with fanbeam high-resolution collimators and 159 keV  $\pm$  10% of the photo window in 90 projections with 360° rotation (128  $\times$  128 matrix). Errors

in timing the beginning of early and delayed SPECT were kept within 3 min in all cases.

#### Image reconstruction

The raw projection data were prefiltered with a Butterworth filter (cutoff frequency: 0.13 cycle/pixel; power factor: 8). The SPECT images were then reconstructed by a filtered backprojection algorithm. Attenuation correction was performed by assuming an elliptical outline of the head in each slice and uniform attenuation in the head ( $\mu = 0.06$ ). The transaxial images, masked below a 20% threshold, 10.7 mm in thickness, of early and delayed SPECT were displayed for visual analysis and ROI study.

#### Visual analysis and ROI study

The transaxial images were analyzed visually, referring to the early and delayed SPECT images obtained from normal healthy volunteers,<sup>8</sup> at the same time by two observers with over 11 years experience in diagnosis in Nuclear Medicine. The abnormality (decreased or increased activity) on each region was assessed.

#### Washout ratio

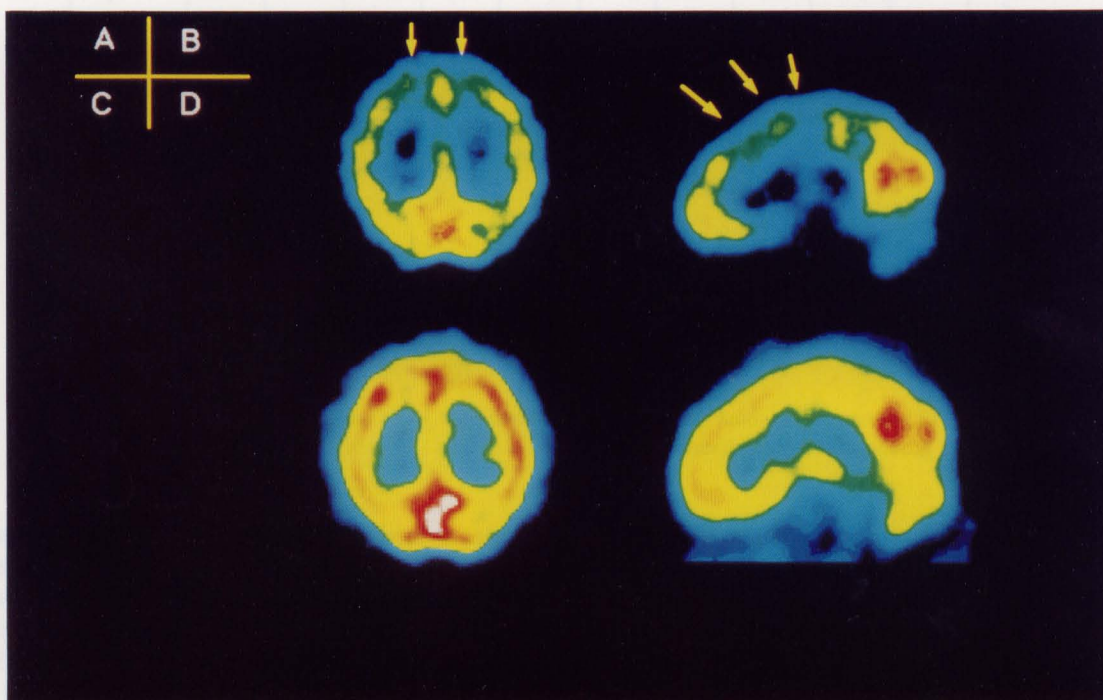
ROIs were outlined in three representative SPECT images corresponding to the level of semioval center (slice A), basal ganglia (slice B) and cerebellum (slice C) (Fig. 1). Irregularly shaped ROIs were placed over the superior frontal cortex (SFC) and parietal cortex (PC) in slice A; the inferior frontal cortex (IFC), temporal cortex (TC) and occipital cortex (OC) in slice B and the cerebellum (CL) in slice C bilaterally. Means of each ROI were obtained, and the washout ratio of each region was calculated. The equation is as follows: I-123 iomazenil

$$\text{washout ratio} = \frac{[(\text{mean of early SPECT counts of a ROI}) - (\text{mean of delayed SPECT counts of the same ROI})]}{(\text{mean of early SPECT counts of a ROI})}$$

**Table 2** Results of the visual analysis of SPECT with I-123-iomazenil in patients mental disorder

Patient no.	Age (yr)	Sex	Disease (The ICD-10 classification)	Benzodiazepine	Early SPECT	Delayed SPECT
1	33	Female	Obsessive-compulsive disorder (F42.2)	Free over 3 m	W.N.L.	W.N.L.
2	30	Female	As above	Free over 1 m	W.N.L.	D* (rt. dorsolateral SFC**)
3	23	Female	As above	Free	W.N.L.	D (rt. dorsolateral SFC)
4	22	Female	As above	Bromazepam 6 mg/day	W.N.L.	W.N.L.
5	29	Male	Somatization disorder (F45.0)	Free	W.N.L.	D (bilateral SFC)
6	31	Female	As above	Free	W.N.L.	W.N.L.
7	22	Female	Bulimia nervosa (F50.2)	Free	W.N.L.	W.N.L.
8	19	Male	Dissociative amnesia (F44.0)	Bromazepam 4 mg/day	W.N.L.	W.N.L.
9	20	Male	Panic disorder (F41.0)	Alprazolam 0.8 mg/day	W.N.L.	D (rt. SFC)
10	39	Female	Generalized anxiety disorder (F41.1)	Alprazolam 1.2 mg/day	W.N.L.	D (bilateral SFC)

\* D: Area of decreased activity, \*\*SFC: Superior frontal cortex



**Fig. 2** The SPECT images in Patient 10 (gAD). A: The delayed I-123 iomazenil transaxial image. The decreased activities were bilaterally recognized in the superior frontal cortex (arrows). B: The delayed sagittal image corresponding to the left arrow on the image A. The decreased activities (arrows) were recognized in the superior frontal cortex. C: The transaxial image of early SPECT corresponding to the slice level of the image A. D: The sagittal image of early SPECT corresponding to the slice level of the image B.

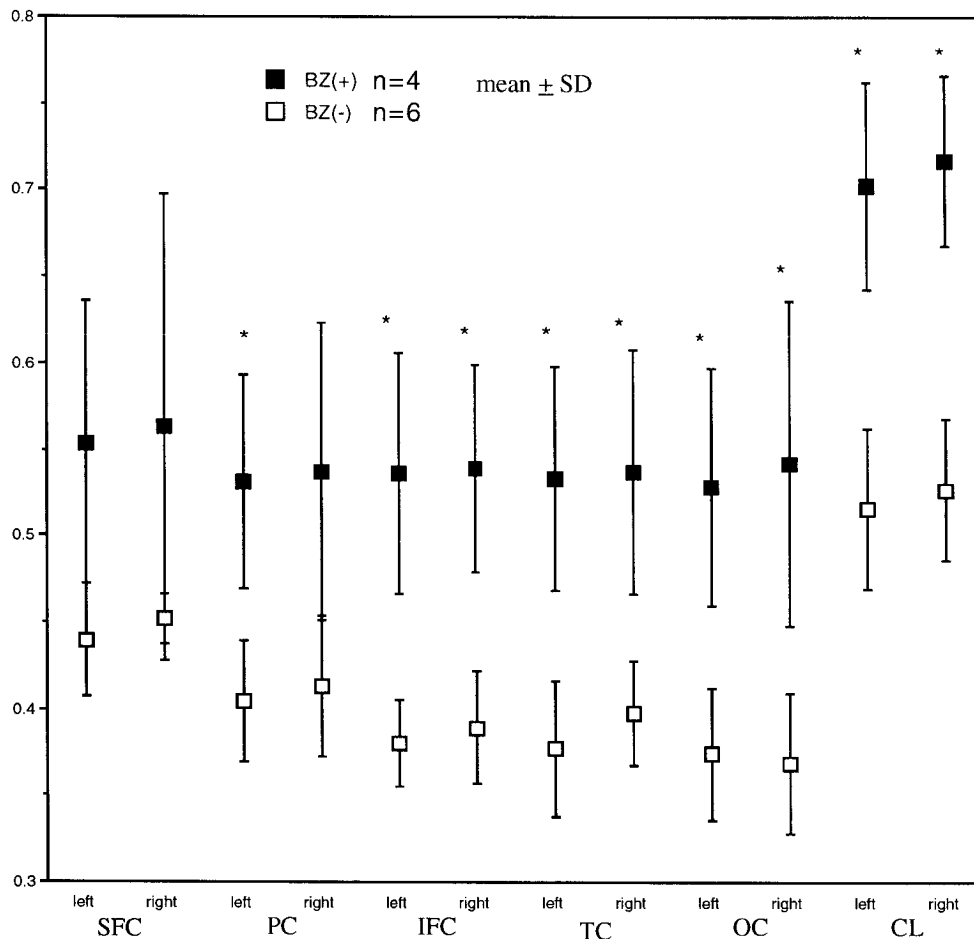
## RESULTS

No side effect was observed after the intravenous administration of I-123 iomazenil.

### Visual analysis (Table 2)

No abnormality was recognized on the early and delayed SPECT in 5 patients [(Patients 1 (OD), 4 (OD), 6 (SD), 7

(BN) and 8 (DA)]. In Patients 2 (OD), 3 (OD) and 9 (PD), the decreased activity in the right superior frontal cortex was recognized on the delayed SPECT. In Patients 5 (SD) and 10 (gAD), the decreased activity was observed in the bilateral frontal cortex on the delayed SPECT (Fig. 2), although the activity of the right side was lower than the left side in Patient 5. The frequencies in appearance of abnormalities were 50% [2 (one with PD and one with



**Fig. 3** I-123 iomazenil washout ratios from the left and right ROIs on the brains of BZ (+) and BZ (-) patient groups with mental disorder.

gAD)/4] in patients who were administered BZ and 50% [3 (2 with OD and one with SD)/6] in patients who were free of BZ.

#### Washout ratio

The washout ratio (means  $\pm$  SD) was higher in the BZ (+) patient group than in the BZ (-) patient group ( $0.56 \pm 0.07$  vs.  $0.45 \pm 0.03$  in SFC,  $0.53 \pm 0.07$  vs.  $0.41 \pm 0.04$  in PC,  $0.54 \pm 0.07$  vs.  $0.39 \pm 0.04$  in TC,  $0.54 \pm 0.08$  vs.  $0.37 \pm 0.04$  in OC and  $0.71 \pm 0.06$  vs.  $0.52 \pm 0.05$  in CL). The rapid washout was recognized in the patients who were administered BZ when compared with the washout in BZ free patients (Fig. 3).

## DISCUSSION

#### Visual analysis

Although the regional cerebral distribution of I-123 iomazenil may chiefly reflect the cerebral blood flow on the early SPECT images, the delayed 2 to 3 hr images reflect mainly the distribution of BZR in the brain.<sup>8,9</sup> The reduced activities on the right and/or left superior frontal

cortex were visually observed in half of the patients on the delayed SPECT in our study, although no abnormal distribution of the tracer was recognized on the early SPECT images in any of the 10 patients. In a patient with gAD who was administered a BZ drug, the late SPECT showed decreased activity in the bilateral frontal cortex (R < L). Feistel et al. reported decreased receptor density in the right hippocampus and left temporal lobe in AD patients with panic attack.<sup>4</sup> Uchiyama et al. evaluated 5 patients with AD by I-123 iomazenil SPECT.<sup>5</sup> They noticed abnormally decreased activity areas on the delayed images in 2 of them; in the left hippocampus and parahippocampal gyrus in one patient and in the right frontal and temporal lobes and the left occipital pole in the other.<sup>5</sup> Schlegel et al. reported that the patients with panic disorder had lower I-123 iomazenil uptake ratios in the frontal, occipital and temporal cortex than patients with epilepsy.<sup>7</sup> Kuikka et al. reported that the mean right-to-left ratio of benzodiazepine receptor uptake in the pre-frontal cortex was significantly higher in 17 unmedicated patients with PD than in the controls.<sup>7</sup> They evaluated the SPECT images at 90 min after injection of I-123

iomazenil.<sup>6,7</sup> All of their subjects (PD) were free of BZ.<sup>6,7</sup> In our patient with PD, the decreased uptake in the right superior frontal cortex was recognized on the delayed SPECT images. She was administered BZ (0.8 mg/day of alprazolam). No morphological abnormality was recognized on MRI. There are no reports about the distribution of I-123 iomazenil in patients with other types of mental disorder. None of our 10 patients had a neurological abnormality. Seven of the ten received X-ray CT and/or MRI and/or perfusion SPECT, but there was no abnormality in any of the findings. In the visual assessment, "abnormality" was judged by comparing the SPECT images with the normal control SPECT images reported by Yonekura et al.<sup>8</sup> Although the tracer distribution in the SPECT images might differ according to the type of equipment, such as the SPECT apparatus, and parameters in data acquisition and processes, they were almost the same in the two institutions. The normal distribution in the delayed images was as follows: The activity was high in the occipital, temporal, frontal and parietal cortex and the cerebellum and was low in pons, caudate nucleus, thalamus and white matter.<sup>8</sup> The reduced activities on the right and/or left superior frontal lobe were visually observed in half of the patients on the delayed SPECT in our study. Although strictly speaking it is difficult to decide the area of the brain with only SPECT images, it is considered that the areas of abnormalities in visual analysis of this study contain the superior part of the prefrontal cortex (perhaps Brodmann area)<sup>9</sup> in all cases. It is widely, though not completely, recognized that the prefrontal cortex plays a significant role in the control of mental functions.<sup>10</sup> There are some reports about the relationship between the prefrontal lobe and neuropsychiatric disorders.<sup>5,7,11-13</sup> There may therefore be a relationship between the some types of mental disorder and the density of BZR in the superior frontal region, but a closer study is needed to evaluate the relationship between the distribution of BZR and mental disorders.

#### Washout rate

Beer et al. reported that the injection of 0.05 mg/kg Anexate containing flumazenil, an antagonist of BZ as an active compound, caused sudden loss of radioactivity in the brain of two volunteers. Thus they concluded that the I-123 iomazenil binding is specific.<sup>1</sup> I-123 iomazenil showed high brain uptake in non-human primates, had a long period of apparent stable steady state concentration in the brain, and approximately 90% of the radioactivity appears to be bound to the benzodiazepine receptors and is capable of being displaced by another benzodiazepine receptor drug.<sup>2</sup> This fact suggests the feasibility of measuring potency by *in vivo* displacement studies after repeated injection of increasing doses of a displacer.<sup>3</sup> With this method, Robert et al. reported that the relative *in vivo* potencies of a series of 5 BZ receptor active drugs (agonists: diazepam, alprazolam and clonazepam, an-

tagonists: Ro 15-1788 and Ro 16-0154) measured in monkeys by means of SPECT was highly correlated with their *in vitro* affinities measured in homogenate binding studies with a radioreceptor assay.<sup>3</sup> The absolute potencies of the agonists appeared remarkably low when compared with those of antagonists, even though the amount of BZ agonists which they used was much greater than the typical therapeutic dose of BZ agonists.<sup>3</sup> With the same method, Sybriska et al. reported that the acute administration of a clinically relevant dose of lorazepam (0.03 mg/kg, i.v.) had no significant effect on the washout of radiotracer from the brain of baboons or humans,<sup>14</sup> but they expected that chronic treatment with BZ may affect the accumulation of the tracer in brain by higher levels of receptor occupancy.<sup>14</sup> In our study, the rapid washout of I-123 iomazenil was recognized in 4 BZ chronically administered patients with mental disorders when compared with those of BZ-free patients. There was no statistically significant difference in the washout only in the SFC. This may be due to the relatively high average washout rate in the SFC when compared with the other ROIs in BZ-free patients. This phenomenon may relate to the results of our visual study showing that the decreased activities in the SFC were recognized in half of the BZ (-) or BZ (+) patients on the delayed SPECT images, but a more thorough study is needed to interpret this phenomenon. The rapid washout of I-123 iomazenil from the brains of BZ (+) patients may be due to the binding effect of the BZ drugs on BZ receptors. The washout ratio of I-123 iomazenil may be one of the objective indicators of a BZ drug effect on mental disorders.

#### ACKNOWLEDGMENT

The Authors thank Toshihiko Yoshinaga, Toyotugu Kiku and Noboru Fukushima for their technical support. We are also very grateful to Nihon Medi-Physics Co., Ltd. for supplying us with I-123 iomazenil.

#### REFERENCES

1. Beer HF, Blauenstein PA, Hasler PH, Delaloye B, Riccabona G, Bangerl I, et al. *In vitro* and *in vivo* evaluation of iodine-123-Ro 16-0154: a new imaging agent for SPECT investigations of benzodiazepine receptors. *J Nucl Med* 31: 1007-1014, 1990.
2. Innis R, Zoghbi S, Johnson E, Woods S, Al-Tikriti M, Baldwin R, et al. SPECT imaging of the benzodiazepine receptor in non-human primate brain with [<sup>123</sup>I]Ro 16-0154. *Eur J Pharmacol* 193: 249-252, 1991.
3. Innis RB, Al-Tikriti MS, Zoghbi S, Baldwin RM, Sybriska EH, Laruelle MA, et al. SPECT imaging of the benzodiazepine receptor: feasibility of *in vivo* potency measurements from stepwise displacement curve. *J Nucl Med* 32: 1754-1761, 1991.
4. Feistel H, Kaschka WP, Ebert D, Koraschky P, Wolf F. Assessment of cerebral benzodiazepine receptor distribu-

- tion in anxiety disorders—A study with I-123-IOMAZENIL. *J Nucl Med* 34: 47, 1993. (abstract)
5. Uchiyama M, Sue H, Fukumitsu N, Mori Y, Kawakami K. Assessment cerebral benzodiazepine receptor distribution in anxiety disorder by <sup>123</sup>I-iomazenil-SPECT: comparison to cerebral perfusion scintigraphy by <sup>123</sup>I-IMP. *Nippon Acta Radiol* 57: 41–46, 1997. (in Japanese)
  6. Schlegel S, Steinert H, Bockisch A, Hahn K, Schloesser R, Benkert O. Decreased benzodiazepine receptor binding in panic disorder measured by IOMAZENIL-SPECT. A preliminary report. *Eur Arch Psychiatry Clin Neurosci* 244 (1): 49–51, 1994.
  7. Kuikka JT, Pitkanen A, Lepola U, Partanen K, Vainio P, Bergstrom KA, et al. Abnormal regional benzodiazepine receptor uptake in the prefrontal cortex in patients with panic disorder. *Nucl Med Commun*. 16 (4): 273–280, 1995.
  8. Yonekura Y, Nishizawa S, Tanaka F, Ishizu K, Okazawa H, Fujita T, et al. Phase I clinical study of <sup>123</sup>I-iomazenil: a new probe to evaluate central-type benzodiazepine receptor with SPECT. *KAKU IGAKU (Jpn J Nucl Med)* 32: 87–97, 1995. (in Japanese)
  9. Onishi Y, Yonekura Y, Tanaka F, Nishizawa S, Okazawa H, Ishizu K, et al. Delayed image of iodine-123 iomazenil as a relative map of benzodiazepine receptor binding: the optimal scan time. *Eur J Nucl Med* 23: 1491–1497, 1996.
  10. Benson DF. *The Neurology of Thinking*. 1st ed., New York: Oxford University Press, 1994.
  11. Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. *J Neuropsychiatry Clin Neurosci* 6 (4): 358–370, 1994.
  12. Goldman-Rakic PS. Working memory dysfunction in schizophrenia. *J Neuropsychiatry Clin Neurosci* 6 (4): 348–357, 1994.
  13. Seidman LJ, Yurgelun-Todd D, Kremen WS, Woods BT, Goldstein JM, Faraone SV, et al. Relationship of prefrontal and temporal lobe MRI measures to neuro-psychological performance in chronic schizophrenia. *Biol Psychiatry* 35 (4): 235–246, 1994.
  14. Sybirska E, Seibyl JP, Bremner JD, Baldwin RM, Al-Tikriti MS, Bradberry C, et al. [<sup>123</sup>I]iomazenil SPECT imaging demonstrates significant benzodiazepine receptor reserve in human and nonhuman primate brain. *Neuropharmacology* 32: 671–680, 1993.