BP_{ND} values for [^{11}C]raclopride studies and k_{ref} values for L-[β-^{11}C]DOPA studies were relatively small (8% for BP_{ND} and 12% for k_{ref} in the striatum), a significant negative correlation was observed between the parameters for both presynaptic and postsynaptic functions. One possible reason for this is the competition between [^{11}C]raclopride and endogenous dopamine at dopamine D_2 receptor sites (Reeves et al., 2007). When the endogenous dopamine synthesis rate measured by PET is either small or large, the concentration of endogenous dopamine in the synaptic cleft must be either low or high, and therefore [^{11}C]raclopride binding to dopamine D_2 receptors might become large or small due to competition with the endogenous dopamine, respectively. Recently, the increases in L-[β-^{11}C]DOPA metabolites, [^{11}C]3,4-dihydroxyphenylacetic acid ([^{11}C]DOPAC) and [^{11}C]homovanillic acid ([^{11}C]HVA) in the extracellular space of the rat striatum after intravenous infusion of L-[β-^{11}C]DOPA was reported using microdialysis, indicating that the endogenous dopamine synthesis rate measured by PET can reflect the concentration of endogenous dopamine in the synaptic cleft (Okada et al., 2011). While interindividual variations of BP_{ND} ($f_{ND}B_{avail}/K_D$) of [^{11}C]raclopride were observed in normal human subjects (Ito et al., 2008), it has been reported that interindividual difference in B_{avail} was significant, but not that in K_D, in human [^{11}C]raclopride PET studies (Farde et al., 1995). This indicates that the interindividual variation of BP_{ND} would be mainly due to the interindividual difference in B_{avail} rather than K_D. B_{avail} is the receptor density available to bind radiotracer *in vivo*, and it might be smaller than the receptor density *in vitro* assays due to the competition with endogenous dopamine (Innis et al., 2007). Thus, the interindividual variation of BP_{ND} would be due to both the interindividual difference in the receptor density and that in the concentration of endogenous dopamine in the synaptic cleft.

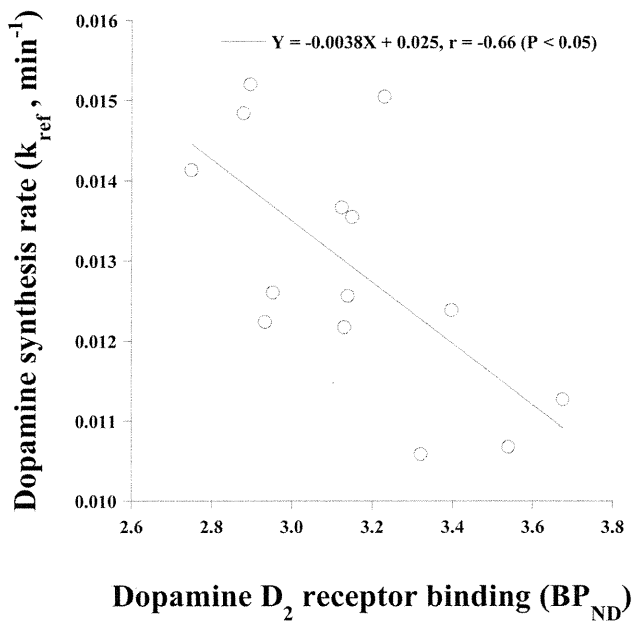

Figure 1. Relation between BP_{ND} of [^{11}C]raclopride studies and k_{ref} of L-[β-^{11}C]DOPA studies in the striatum.

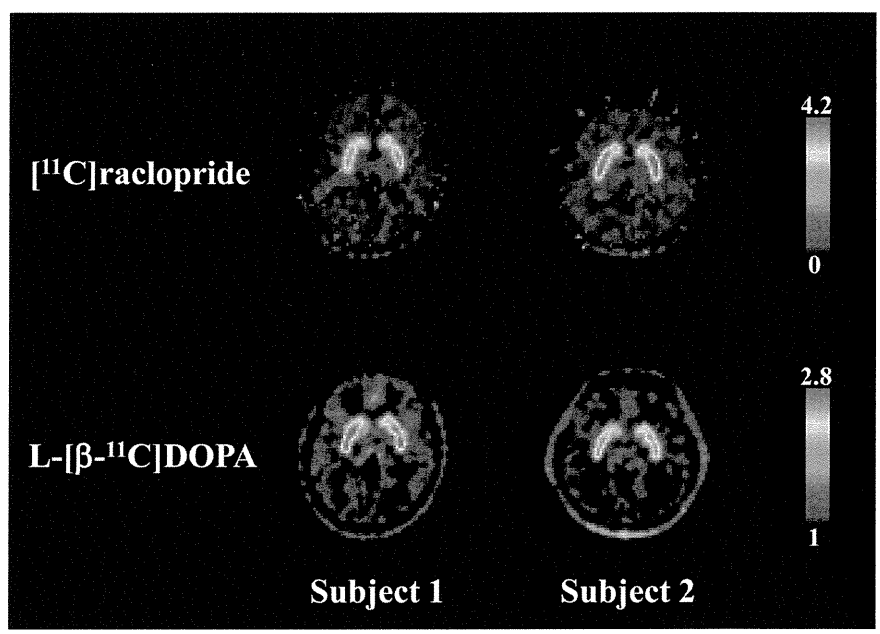

Figure 2. Typical images of BP_{ND} of [^{11}C]raclopride studies for subjects with low and high BP_{ND} (subjects 1 and 2, respectively) and corresponding images indicating dopamine synthesis rate calculated as the ratio of time-integrated radioactivities from 29 to 89 min of L-[β-^{11}C]DOPA studies between brain regions and the occipital cortex (Ito et al., 2007).

Another possible reason for a significant negative correlation between presynaptic and postsynaptic dopaminergic functions might be a compensative relation between the two functions. The mechanism for the regulation of dopamine release from presynapse has been explained by both phasic and tonic dopamine release (Grace, 1991). Phasic dopamine release would be caused by firing of dopaminergic neuron, and tonic dopamine release would set the background level of dopamine receptor stimulation. If the endogenous dopamine synthesis ability at rest condition measured by L-[β-^{11}C]DOPA PET can indicate tonic dopamine release, the background level of dopamine receptor stimulation by tonic dopamine release might be compensatively related to the dopamine D_2 receptor density, indicating that the tone of dopaminergic neurotransmission might not be so different between subjects. In addition, the TaqIA1 allele of dopamine D_2 receptor gene has been reported to be associated with a low density of dopamine D_2 receptors (Jönsson et al., 1999) and with increased striatal activity of AADC in healthy human subjects (Laakso et al., 2005), supporting our present results. They attempted to explain these findings by a lower dopamine D_2 receptor expression leading to decreased autoreceptor function, and therefore increased dopamine synthesis. However, further studies, including animal studies *in vitro* and *in vivo*, will be required to explain the negative correlation between presynaptic and postsynaptic dopaminergic functions in the present study.

Increased striatal dopamine synthesis rate in neuroleptic-naive or -free patients with schizophrenia has been reported using PET with L-[β-^{11}C]DOPA (Lindström et al., 1999; Nozaki et al., 2009) or 6-[^{18}F]fluoro-L-DOPA (Hietala et al., 1995). On the other hand, no significant change in striatal dopamine D_2 receptor density in patients with schizophrenia has been reported using PET with [^{11}C]raclopride (Farde et al., 1990). It might be

valuable to investigate the relation between presynaptic and postsynaptic dopaminergic functions in patients with schizophrenia whether such compensative relation in the striatum was evident or disrupted in patients.

It has been reported that the dopamine D_2 receptor density measured by PET with [^{11}C]raclopride was significantly correlated with a certain personality trait, the detachment score of Karolinska Scales of Personality (Farde et al., 1997; Breier et al., 1998), while no significant correlation was observed between the endogenous dopamine synthesis rate measured by PET with 6-[^{18}F]fluoro-L-DOPA and the detachment score (Laakso et al., 2003). On the other hand, endogenous dopamine synthesis was significantly correlated with anxiety-related personality scales of Karolinska Scales of Personality (Laakso et al., 2003). These findings indicate that dopamine D_2 receptor density and the endogenous dopamine synthesis rate might be related to personality traits independently, although a significant negative correlation was observed between parameters for both presynaptic and postsynaptic functions in the present study. The relations between personality traits and presynaptic or postsynaptic dopaminergic functions should be further investigated in large series of subjects.

NAAs are transported by the neutral amino acid carrier system in the blood–brain barrier in a competitive fashion (Oldendorf, 1971; Pardridge, 1977; Ito et al., 1995), and the competitive transport of L-DOPA with NAAs at the blood–brain barrier has been revealed (Ito et al., 2006). We have previously reported a significant negative correlation between the weighted sum of the NAAs and the overall uptake rate constant of L-[β-^{11}C]DOPA calculated using the arterial input function (Ito et al., 2006). The overall uptake rate constant calculated using the arterial input function includes the influx rate constant at the blood–brain barrier, and therefore negatively correlated with the weighted sum of the NAAs due to the competitive transport at the blood–brain barrier. In the present study, no significant correlation was observed between the weighted sum of NAAs in plasma and the dopamine synthesis rate k_{ref} of L-[β-^{11}C]DOPA. Because k_{ref} is calculated using time–activity data in a reference brain region, not in arterial plasma, this parameter does not reflect the influx rate constant at the blood–brain barrier (Ito et al., 2006, 2007). Thus, the dopamine synthesis rate k_{ref} of L-[β-^{11}C]DOPA is independent of the NAA concentration.

In conclusion, a significant negative correlation was observed between parameters for both presynaptic and postsynaptic dopaminergic functions in the striatum of normal human subjects. Although the interindividual variation of BP_{ND} would be due to both the interindividual difference in the receptor density and that in the concentration of endogenous dopamine in the synaptic cleft, this relation might indicate a compensative relation between the two functions. Further studies to elucidate the interindividual variation in dopaminergic neurotransmission tone of neuropsychiatric disorders will be required.

References

Breier A, Kestler L, Adler C, Elman I, Wiesenfeld N, Malhotra A, Pickar D (1998) Dopamine D_2 receptor density and personal detachment in healthy subjects. Am J Psychiatry 155:1440–1442.

Brix G, Zaers J, Adam LE, Bellemann ME, Ostertag H, Trojan H, Haberkorn U, Doll J, Oberdorfer F, Lorenz WJ (1997) Performance evaluation of a whole-body PET scanner using the NEMA protocol. J Nucl Med 38:1614–1623.

Brown RM, Crane AM, Goldman PS (1979) Regional distribution of monoamines in the cerebral cortex and subcortical structures of the rhesus monkey: concentrations and in vivo synthesis rates. Brain Res 168: 133–150.

Farde L, Ehrin E, Eriksson L, Greitz T, Hall H, Hedström CG, Litton JE, Sedvall G (1985) Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. Proc Natl Acad Sci U S A 82:3863–3867.

Farde L, Halldin C, Stone-Elander S, Sedvall G (1987) PET analysis of human dopamine receptor subtypes using ^{11}C-SCH 23390 and ^{11}C-raclopride. Psychopharmacology 92:278–284.

Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordström AL, 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.

Farde L, Hall H, Pauli S, Halldin C (1995) Variability in D_2-dopamine receptor density and affinity: a PET study with [^{11}C]raclopride in man. Synapse 20:200–208.

Farde L, Gustavsson JP, Jönsson E (1997) D_2 dopamine receptors and personality traits. Nature 385:590.

Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RS (1990) The relationship between global and local changes in PET scans. J Cereb Blood Flow Metab 10:458–466.

Gjedde A (1988) Exchange diffusion of large neutral amino acids between blood and brain. In: Peptide and amino acid transport mechanisms in the cerebral nervous system (Rakic L, Begley DJ, Davson H, Zlokovic BV, eds), pp 209–217. New York: Stockton.

Gjedde A, Reith J, Dyve S, Léger G, Guttman M, Diksic M, Evans A, Kuwabara H (1991) Dopa decarboxylase activity of the living human brain. Proc Natl Acad Sci U S A 88:2721–2725.

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24.

Halldin C, Stone-Elander S, Farde L, Ehrin E, Fasth KJ, Långström B, Sedvall G (1986) Preparation of ^{11}C-labelled SCH 23390 for the in vivo study of dopamine D-1 receptors using positron emission tomography. Int J Rad Appl Instrum A 37:1039–1043.

Hartvig P, Agren H, Reibring L, Tedroff J, Bjurling P, Kihlberg T, Långström B (1991) Brain kinetics of L-[β-^{11}C]dopa in humans studied by positron emission tomography. J Neural Transm Gen Sect 86:25–41.

Heinz A, Siessmeier T, Wrase J, Buchholz HG, Gründer G, Kumakura Y, Cumming P, Schreckenberger M, Smolka MN, Rösch F, Mann K, Bartenstein P (2005) Correlation of alcohol craving with striatal dopamine synthesis capacity and $D_{2/3}$ receptor availability: a combined [^{18}F]DOPA and [^{18}F]DMFP PET study in detoxified alcoholic patients. Am J Psychiatry 162:1515–1520.

Hietala J, Syvälahti E, Vuorio K, Räkköläinen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Kirvelä O, Ruotsalainen U, Salokangas RKR (1995) Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346:1130–1131.

Huang SC, Yu DC, Barrio JR, Grafton S, Melega WP, Hoffman JM, Satyamurthy N, Mazziotta JC, Phelps ME (1991) Kinetics and modeling of L-6-[^{18}F]fluoro-dopa in human positron emission tomographic studies. J Cereb Blood Flow Metab 11:898–913.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, et al. (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539.

Ito H, Hatazawa J, Murakami M, Miura S, Iida H, Bloomfield PM, Kanno I, Fukuda H, Uemura K (1995) Aging effect on neutral amino acid transport at the blood-brain barrier measured with L-[2-^{18}F]-fluorophenylalanine and PET. J Nucl Med 36:1232–1237.

Ito H, Hietala J, Blomqvist G, Halldin C, Farde L (1998) Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [^{11}C]raclopride binding. J Cereb Blood Flow Metab 18:941–950.

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-[β-^{11}C]DOPA. Nucl Med Commun 27:723–731.

Ito H, Shidahara M, Takano H, Takahashi H, Nozaki S, Suhara T (2007) Mapping of central dopamine synthesis in man using positron emission tomography with L-[β-^{11}C]DOPA. Ann Nucl Med 21:355–360.

Ito H, Takahashi H, Arakawa R, Takano H, Suhara T (2008) Normal data-

base of dopaminergic neurotransmission system in human brain measured by positron emission tomography. Neuroimage 39:555–565.

Jönsson E, Sedvall G, Brené S, Gustavsson JP, Geijer T, Terenius L, Crocq MA, Lannfelt L, Tylec A, Sokoloff P, Schwartz JC, Wiesel FA (1996) Dopamine-related genes and their relationships to monoamine metabolites in CSF. Biol Psychiatry 40:1032–1043.

Jönsson EG, Nöthen MM, Grünhage F, Farde L, Nakashima Y, Propping P, Sedvall GC (1999) Polymorphisms in the dopamine D_2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 4:290–296.

Kienast T, Siessmeier T, Wrase J, Braus DF, Smolka MN, Buchholz HG, Rapp M, Schreckenberger M, Rösch F, Cumming P, Gruender G, Mann K, Bartenstein P, Heinz A (2008) Ratio of dopamine synthesis capacity to D_2 receptor availability in ventral striatum correlates with central processing of affective stimuli. Eur J Nucl Med Mol Imaging 35:1147–1158.

Köhler C, Hall H, Ogren SO, Gawell L (1985) Specific in vitro and in vivo binding of ^{3}H-raclopride. A potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. Biochem Pharmacol 34:2251–2259.

Laakso A, Wallius E, Kajander J, Bergman J, Eskola O, Solin O, Ilonen T, Salokangas RK, Syvälahti E, Hietala J (2003) Personality traits and striatal dopamine synthesis capacity in healthy subjects. Am J Psychiatry 160:904–910.

Laakso A, Pohjalainen T, Bergman J, Kajander J, Haaparanta M, Solin O, Syvälahti E, Hietala J (2005) The A1 allele of the human D_2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. Pharmacogenet Genomics 15:387–391.

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

Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ, Frackowiak RS (1996) Comparison of methods for analysis of clinical [^{11}C]raclopride studies. J Cereb Blood Flow Metab 16:42–52.

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

Lloyd KG, Hornykiewicz O (1972) Occurrence and distribution of aromatic L-amino acid (L-DOPA) decarboxylase in the human brain. J Neurochem 19:1549–1559.

Nagatsu T (1991) Genes for human catecholamine-synthesizing enzymes. Neurosci Res 12:315–345.

Nozaki S, Kato M, Takano H, Ito H, Takahashi H, Arakawa R, Okumura M, Fujimura Y, Matsumoto R, Ota M, Takano A, Otsuka A, Yasuno F, Okubo Y, Kashima H, Suhara T (2009) Regional dopamine synthesis in patients with schizophrenia using L-[β-^{11}C]DOPA PET. Schizophr Res 108:78–84.

Okada M, Nakao R, Hosoi R, Zhang MR, Fukumura T, Suzuki K, Inoue O (2011) Microdialysis with radiometric monitoring of L-[β-^{11}C]DOPA to assess dopaminergic metabolism: effect of inhibitors of L-amino acid decarboxylase, monoamine oxidase, and catechol-O-methyltransferase on rat striatal dialysate. J Cereb Blood Flow Metab 31:124–131.

Oldendorf WH (1971) Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am J Physiol 221:1629–1639.

Pardridge WM (1977) Kinetics of competitive inhibition of neutral amino acid transport across the blood-brain barrier. J Neurochem 28:103–108.

Patlak CS, Blasberg RG (1985) Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab 5:584–590.

Reeves SJ, Mehta MA, Montgomery AJ, Amiras D, Egerton A, Howard RJ, Grasby PM (2007) Striatal dopamine (D_2) receptor availability predicts socially desirable responding. Neuroimage 34:1782–1789.

Sugaya Y, Sasaki Y, Goshima Y, Kitahama K, Kusakabe T, Miyamae T, Kato T, Misu Y (2001) Autoradiographic studies using L-[^{14}C]DOPA and L-DOPA reveal regional Na^+-dependent uptake of the neurotransmitter candidate L-DOPA in the CNS. Neuroscience 104:1–14.

Tedroff J, Aquilonius SM, Hartvig P, Lundqvist H, Bjurling P, Långström B (1992) Estimation of regional cerebral utilization of [^{11}C]-L-3,4-dihydroxyphenylalanine (DOPA) in the primate by positron emission tomography. Acta Neurol Scand 85:166–173.

Watson CC, Newport D, Casey ME (1996) A single scatter simulation technique for scatter correction in 3D PET. In: Three-dimensional image reconstruction in radiology and nuclear medicine (Grangeat P, Amans JL, eds), pp 255–268. Dordrecht, The Netherlands: Kluwer Academic.

JCBFM Open

Journal of Cerebral Blood Flow & Metabolism (2012), 1–11

www.jcbfm.com

Review Article

Functional significance of central D1 receptors in cognition: beyond working memory

Hidehiko Takahashi[1,2,3], Makiko Yamada[2,3] and Tetsuya Suhara[2]

[1]*Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, Japan;* [2]*Department of Molecular Neuroimaging, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan;* [3]*Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Saitama, Japan*

The role of dopamine D1 receptors in prefrontal cortex function, including working memory, is well acknowledged. However, relatively little is known about their role in other cognitive or emotional functions. We measured both D1 and D2 receptors in the brain using positron emission tomography in healthy subjects, with the aim of elucidating how regional D1 and D2 receptors are differentially involved in cognitive and emotional functions beyond working memory. We found an inverted U-shaped relation between prefrontal D1 receptor availability and Wisconsin Card Sorting Test performance, indicating that too little or too much D1 receptor stimulation impairs working memory or set shifting. In addition, variability of D1 receptor availability in the amygdala and striatum was related to individual differences in emotional responses and decision-making processes, respectively. These observations suggest that the variability of available D1 receptors might be associated with individual differences in brain functions that require phasic dopamine release. An interdisciplinary approach combining molecular imaging of dopamine neurotransmission with cognitive neuroscience and clinical psychiatry will provide new perspectives for understanding the neurobiology of neuropsychiatric disorders such as schizophrenia, addiction and Parkinson's disease, as well as novel therapeutics for cognitive impairments observed in them.
Journal of Cerebral Blood Flow & Metabolism advance online publication, 11 January 2012; doi:10.1038/jcbfm.2011.194

Keywords: cognition; D1 receptors; dopamine; positron emission tomography; psychiatry

Positron emission tomography imaging of D1 and D2 receptors and working memory

Because dopamine D1 receptors in the prefrontal cortex (PFC) are several times more abundant than D2 receptors (Hall *et al*, 1994), the relationship between D1 receptors and PFC functions has been widely investigated. Sawaguchi and Goldman-Rakic (1994) showed that local administration of D1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate. In human, Müller *et al* (1998) reported that systemic administration of a mixed D1/D2 agonist facilitated working memory while the selective D2 agonist had no effect, indicating that the dopaminergic modulation of working memory processes is mediated primarily via D1 receptors.

In contrast to D1 receptors, relatively less attention has been paid to the role of prefrontal D2 receptors in cognitive functions partly because their density in extrastriatal regions is very low (Suhara *et al*, 1999). It was reported that blockade of D2 receptors in PFC did not impair working memory in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994), but some human studies reported that systemic administration of D2 agonist or antagonist modulated cognitive functions that are subserved by PFC (McDowell *et al*, 1998; Mehta *et al*, 1999). We measured both D1 and extrastriatal D2 receptor availabilities (binding potentials), indices proportional to receptor density, using [^{11}C]SCH23390 and [^{11}C]FLB457 positron emission tomography (PET), respectively, in healthy male subjects, and aimed to

Correspondence: Professor H Takahashi, Department of Psychiatry, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail: hidehiko@kuhp.kyoto-u.ac.jp
Received 14 September 2011; revised 2 November 2011; accepted 2 November 2011

elucidate how regional D1 and D2 receptors are differentially involved in neurocognitive performance including frontal lobe functions. Receptor availability is defined as receptors that are available to be bound by the radiotracer. This means receptors that are available for stimulation by released endogenous dopamine.

A body of animal studies has indicated that stimulation of D1 receptors in PFC produces an inverted U-shaped dose–response curve, such that too little or too much D1 receptor stimulation impairs PFC functions (Cools and D'Esposito, 2011; Goldman-Rakic *et al*, 2000; Williams and Castner, 2006). Therefore, we conducted quadratic regression analysis to reveal the putative 'U-shaped' relation between D1 receptor availability in PFC and PFC function. Although standard linear regression analysis revealed a trend-level negative correlation between D1 receptor availability in PFC and total error of the Wisconsin Card Sorting Test (WCST), a test requiring working memory and set-shifting abilities, a quadratic regression model better predicted the relation (Takahashi *et al*, 2008). That is, we found a significant 'U-shaped' relation between D1 receptor availability in PFC and total error of WCST (because total error of WCST is a negative measure of frontal lobe function, the relation is not 'inverted'; Figures 1A and 1B). However, neither linear nor quadratic relation was found between D2 receptor availability in PFC and any neuropsychological measures.

Primal animal studies indicated that stimulation of D1 receptors in PFC produces an inverted U-shaped response in working memory, with the response being optimized within a narrow range of D1 receptor stimulation (Castner and Goldman-Rakic, 2004; Goldman-Rakic *et al*, 2000; Lidow *et al*, 2003; Seamans and Yang, 2004; Vijayraghavan *et al*, 2007). Subsequent human studies have investigated the effect of a functional polymorphism in the catechol O-methyltransferase gene, which has been shown to modulate the prefrontal dopamine level, on prefrontal function. Catechol O-methyltransferase gene contains a common polymorphism, a valine (Val)-to-methionine (Met) substitution at codon 158 (Val158Met). The Val allele is associated with higher activity, whereas the Met allele is associated with lower enzymatic activity. Consequently, Val carriers have a lower level of extracellular dopamine in PFC. A PET study using [^{11}C]NNC112 has demonstrated that Val carriers show significantly higher cortical D1 receptor availability than Met carriers, and the authors suggested a mechanism in which a lower level of extracellular dopamine in PFC induces upregulation of D1 receptors in Val carriers (Slifstein *et al*, 2008). Val carriers show lower performance and increased (inefficient) PFC activation during completion of cognitive tasks related to PFC functions (WCST and N-back task) (Egan *et al*, 2001; Goldberg *et al*, 2003). It was reported that amphetamine challenge in Val carriers induced improvement in the performance of WCST and decreased (efficient) PFC activation during N-back task, whereas that in Met carriers caused deterioration in the performance of WCST and increased (inefficient) PFC activation, indicating that too little or too much dopamine signaling would impair PFC functions, although these studies could not identify the receptor subtype that has a central role in this effect (Mattay *et al*, 2003; Williams-Gray *et al*, 2007).

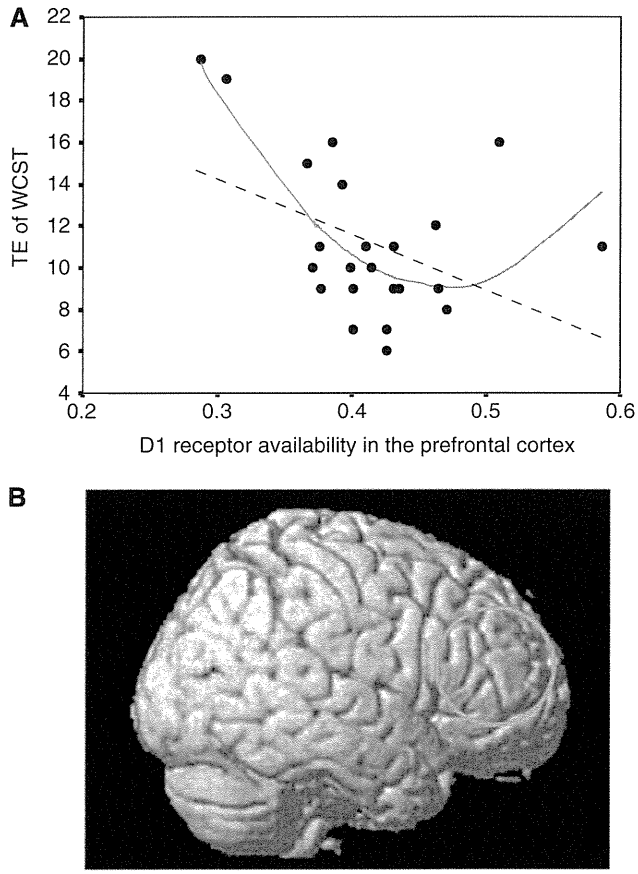

Figure 1 Quadratic (inverted U-shaped) relation between D1 receptor availability in prefrontal cortex (PFC) and performance of Wisconsin Card Sorting Test (WCST). (**A**) Region of interest (ROI) analysis revealed a significant quadratic regression between D1 receptor availability in PFC and total error (TE) of WCST. Red solid line: quadratic regression, black broken line: linear regression. (**B**) Statistical parametric mapping (SPM) analysis also revealed significant quadratic regression between prefrontal D1 receptor availability and total error of WCST.

We first showed an inverted U-shaped relation between D1 receptors in PFC and executive function including working memory in normal healthy subjects (Takahashi *et al*, 2008). An inverted U-shaped response has been suggested based on cognitive and behavioral studies, but the exact physiological mechanism of this effect has not yet been fully understood. A recent monkey electrophysiology study has demonstrated a neuron-level mechanism that constitutes the inverted U-shaped response

whereby too much or too little stimulation of prefrontal D1 receptors leads to working memory deficits. D1 receptor stimulation had a suppressive effect on the PFC neural activities involved in a spatial working memory task. Moderate D1 receptor stimulation spatially tunes PFC neurons that process target signals by preferentially suppressing nontarget (noisy) neural activities, whereas excessive D1 receptor stimulation induces nonselective suppression of PFC neural activities irrespective of whether the neural activities are task related or not (Vijayraghavan *et al*, 2007).

Animal studies have suggested that the inverted U-shaped principle of D1 receptor stimulation mediating working memory does not necessarily apply to other prefrontal functions (Floresco and Magyar, 2006). In fact, except for WCST, we did not find any association between D1 receptor availability and prefrontal functions less dependent on the working memory process (word fluency task by phonetic or semantic cues and problem-solving test; Takahashi *et al*, 2008).

Recently, McNab *et al* (2009) showed the quadratic relation between the improvement of working memory capacity by training and the change in D1 receptor availability induced by training, although greater reduction in D1 receptor availability was associated with greater improvements in working memory capacity within the measured range. However, a recent study showed that age-related reduction in D1 receptor availability in PFC was associated with age-related reduction in working memory performance and PFC activation during working memory load (Bäckman *et al*, 2011), indicating that other factors besides D1 receptor availability, such as cerebrovascular pathology, could influence the PFC functions and PFC activation during working memory load in older adults. Furthermore, although [^{11}C]SCH23390 and [^{11}C]NNC112 are selective radioligands for D1 receptors, they have some affinity for 5HT2A receptors. 5HT2A receptor density in the striatum is negligible compared with D1 receptor density, whereas 5HT2A receptor density is not negligible in the extrastriatal regions. Previous reports in the literature have indicated that their affinity for 5HT2A receptors relative to D1 receptors is negligible, and recent *in-vivo* studies reported that $\sim$10% to 25% of the cortical signals of these radioligands were due to binding to 5HT2A receptors. Thus, cautious interpretation of the extrastriatal findings regarding these radioligands is recommended (Ekelund *et al*, 2007; Slifstein *et al*, 2007).

In line with our previous study (Takahashi *et al*, 2007), we also found that D2 receptor availability in the hippocampus (HPC) was positively correlated not only with episodic memory ability but also with WCST performance (Takahashi *et al*, 2008). Patients with lesions in HPC sometimes show deficits in WCST (Corkin, 2001; Igarashi *et al*, 2002). These observations suggest that hippocampal D2 receptors could modulate PFC activity by the HPC–PFC pathway, which has a significant role in the cognitive process (Laroche *et al*, 2000; Thierry *et al*, 2000). Accumulating evidence has suggested the modulatory effects of dopamine on HPC–PFC interactions (Aalto *et al*, 2005; Goto and Grace, 2008; Seamans *et al*, 1998; Tseng *et al*, 2007). Conceivably, dopamine influences PFC neurons directly by prefrontal D1 receptors and indirectly by hippocampal D2 receptors via the HPC–PFC pathway. Supporting the importance of hippocampal D2 receptors in PFC functions, MacDonald *et al* (2009) reported that lower D2 receptor availability in HPC was associated with greater intraindividual variability in episodic memory and executive function, indicating that lower D2 receptor-mediated transmission in HPC leads to noisy neural information processing and results in unstable episodic memory and executive functions.

Müller *et al* (1998) reported that the systemic administration of the mixed D1/D2 agonist pergolide facilitated working memory while the selective D2 agonist bromocriptine had no effect. However, there is converging evidence from human and animal studies to suggest the involvement of D2 receptors in cognitive functions. It was reported that the systemic administration of the D2 agonist bromocriptine in human improved cognitive functions including working memory and executive functions (McDowell *et al*, 1998), and the administration of the D2 antagonist sulpiride impaired those functions (Mehta *et al*, 1999). In an animal study, mice lacking D2 receptors were reported to have a working memory deficit (Glickstein *et al*, 2002). These studies, however, did not reveal the regions most responsible for these effects. Moreover, although the involvement of D1 receptors in working memory is widely recognized, it was not clear whether D1 receptor stimulation alone or the combination of D1 and D2 receptor stimulation is most effective. Positron emission tomography findings including ours suggested that orchestration of prefrontal D1 receptors and hippocampal D2 receptors might be necessary for normal prefrontal functions (MacDonald *et al*, 2009; Takahashi *et al*, 2007, 2008).

Positron emission tomography imaging of D1 and D2 receptors and amygdala function

The amygdala has a central role in processing affective stimuli, and in particular, threatening stimuli in the brain (LeDoux, 2000). The amygdala receives a moderate innervation of dopaminergic fibers (Asan, 1998), and dopamine D1 and D2 receptors are moderately expressed in this region (Ito *et al*, 2008). Dopamine release in the amygdala is increased in response to stress (Inglis and Moghaddam, 1999). It has been shown in animal studies that dopamine potentiates the response of the amygdala

by augmenting excitatory sensory input and attenuating inhibitory prefrontal input to the amygdala (Rosenkranz and Grace, 2002). A human functional magnetic resonance imaging (fMRI) study reported that dopaminergic drug therapy such as levodopa or dopamine agonists partially restored amygdala activation due to emotional task in Parkinson's disease patients who showed no significant amygdala activation during drug-off states (Tessitore *et al*, 2002). In addition, another fMRI study of healthy volunteers has demonstrated that amphetamine potentiated the response of the amygdala during an emotional task (Hariri *et al*, 2002). More recently, Kienast *et al* (2008) reported that dopamine storage capacity in human amygdala, measured with 6-[(^{18})F]fluoro-L-DOPA PET, was positively correlated with fMRI signal changes in the amygdala. However, contribution of dopamine D1 and D2 receptors to amygdala activation in response to affective stimuli is unknown in human. To investigate the relation between amygdala activation and dopamine receptor subtype, we conducted a multimodal *in-vivo* neuroimaging study in which dopamine D1 and D2 receptor availabilities in the amygdala were measured with PET, and amygdala activation in response to fearful stimuli was assessed by fMRI (Takahashi *et al*, 2010*b*). Healthy male subjects, a different cohort from that of our study described in the previous section, underwent fMRI for measuring the amygdala response to fearful faces, after which both D1 and D2 receptors in the amygdala were measured using PET with [^{11}C]SCH23390 and [^{11}C]FLB457, respectively.

Although robust bilateral amygdala activations induced by fearful faces were identified in a group analysis, there was considerable individual difference in the degree of amygdala activation. Similarly, although moderate levels of D1 and D2 receptors in the amygdala were measured, notably high variances in both receptor availabilities were observed. Importantly, D1 receptor availability in the amygdala was not correlated with D2 receptor availability in the amygdala. Both voxelwise statistical parametric mapping analysis and regions of interest analysis revealed that blood oxygen level-dependent signals in the amygdala induced by fearful faces were positively correlated with D1 receptor availability, but not with D2 receptor availability, in the amygdala (Figures 2A and 2B; Takahashi *et al*, 2010*b*). That is, individuals with high D1 receptor density in the amygdala tend to show greater amygdala activation in response to fearful stimuli.

In rat studies, Rosenkranz and Grace (2002) showed that dopamine enhances the response of the amygdala by augmenting excitatory sensory input via dopamine D2 receptor stimulation and attenuating inhibitory prefrontal input to the amygdala through dopamine D1 receptor stimulation. More recently, several studies showed that both D1 and D2 receptor stimulations directly enhanced the excitability of amygdala projection neurons via postsynaptic mechanism (Kroner *et al*, 2005; Rosenkranz and Grace, 2002; Yamamoto *et al*, 2007). Amygdala projection neurons are under inhibitory control by GABAergic interneurons (Royer *et al*, 1999). Both projection neurons and interneurons in the amygdala express dopamine D1 and D2 receptors (Rosenkranz and Grace, 1999). Dopamine and D1 receptor agonist have been shown to augment interneuron excitability and increase the frequency of inhibitory postsynaptic current in amygdala projection neurons (Kroner *et al*, 2005). This is a counterintuitive result, considering the fact that dopamine disinhibits amygdala response *in vivo*. However, Marowsky *et al* (2005) found that a

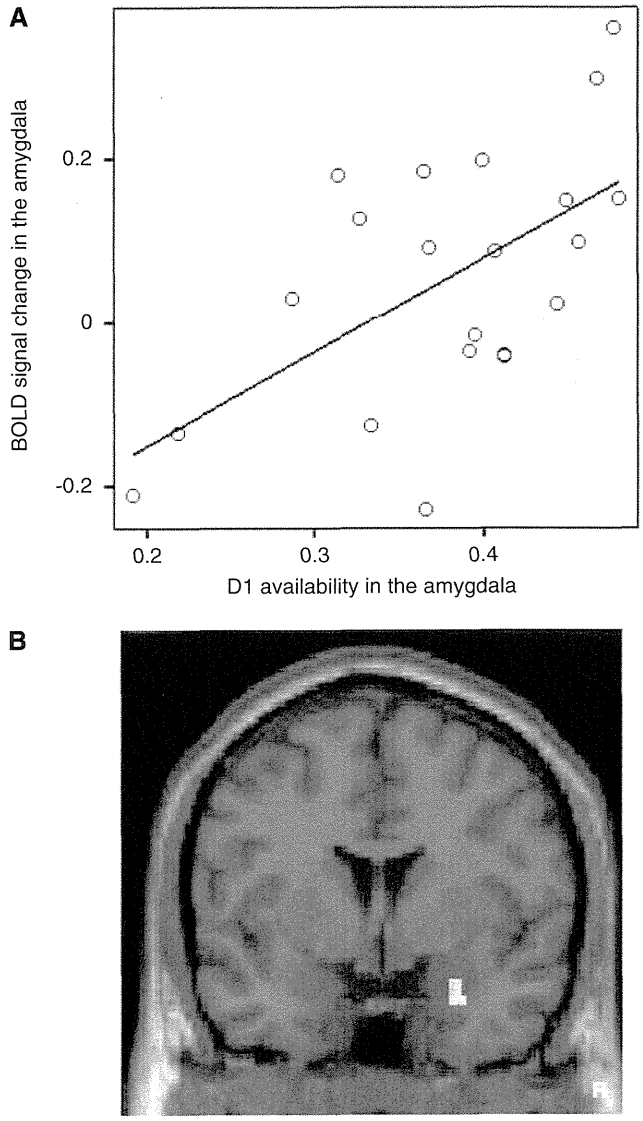

Figure 2 (**A**) Regions of interest (ROIs) correlation analysis revealed significant positive correlations between D1 receptor availability in the amygdala and the degree of amygdala activation. (**B**) Statistical parametric mapping (SPM) correlation analysis also revealed similar correlations. R indicates right.

subpopulation of amygdala interneurons (paracapsular intercalated cells), located between the major input and output stations of the amygdala, is suppressed by dopamine through D1 receptor stimulation. Dopamine D2 receptors also have a role in disinhibiting amydala response by decreasing inhibition onto projection neurons and increasing inhibition onto interneurons (Bissiere *et al*, 2003). As described above, not only dopamine D1 but also D2 receptors contribute to potentiating amygdala response via various mechanisms. In fact, our previous pharmacological fMRI study reported that systemic administration of selective dopamine D2 receptor antagonist attenuated amygdala activation in response to fearful stimuli (Takahashi *et al*, 2005). However, as selective dopamine D1 receptor antagonist for clinical use is not available, we cannot directly compare which D1 or D2 antagonist is more efficient in attenuating amygdala response.

Using a multimodality *in-vivo* neuroimaging approach and dual radioligands, we could for the first time directly compare amygdala dopamine D1 and D2 receptor availabilities with amygdala response evoked by fearful stimuli in human. Although the more detailed mechanism needs to be clarified in future investigations including animal studies, our study suggested that dopamine D1 receptors have a major role in the overall potentiation of amygdala response. At the behavioral level, a number of animal studies have reported that systemic and local applications of D1 agonist (or antagonist) into the amygdala potentiate (or decrease) fear response in animals. Although some studies reported that applications of D2 agonist and antagonist induced similar effects, the results were less consistent compared with D1-mediated effects (for review, see de la Mora *et al*, 2010 and Pezze and Feldon, 2004). Thus, our finding could be regarded as being consistent with previous behavioral pharmacological studies. The combination of PET molecular imaging and fMRI seems to represent a powerful approach for understanding molecular functions in affective neuroscience.

Positron emission tomography imaging of D1 and D2 receptors and decision making under risk

Decision making under risk has been studied in philosophy, psychology, and economics throughout the last century. Normative economic theories (e.g., expected utility theory) assume that individuals are rational decision makers and have purely self-regarding preferences. However, we sometimes make boundedly rational decisions (altruistic behavior, moral judgment, gamble, etc.), which are not accounted for by normative economic theories. Behavioral or experimental economics studies have shown a substantial body of field and empirical evidence that decision makers systematically depart from Camerer and Loewenstein (2004). One type of systematic departure is that subjective weights on probabilities appear to be nonlinear: people often overestimate low probabilities (e.g., playing lotteries) and underestimate high probabilities. A leading alternative to the expected utility theory is the prospect theory (Tversky and Kahneman, 1992). The central feature of the prospect theory is nonlinear probability weighting. Objective probabilities, p, are transformed nonlinearly into decision weights $w(p)$ by a weighting function. In an inverse S-shaped nonlinear weighting function, low probabilities are overweighted and moderate-to-high probabilities are underweighted. The function neatly explains the typically observed pattern of risk seeking for low-probability gain and risk aversion toward high-probability gain.

A synthesis of economics and neuroscience is called neuroeconomics. Neuroeconomics fMRI studies have demonstrated the neural basis for boundedly rational decision makings under risk, including some features of the prospect theory (De Martino *et al*, 2006; Tom *et al*, 2007). A deeper question is how modulatory neurotransmission is involved in the central process of these boundedly rational decision makings (Fox and Poldrack, 2009; Rangel *et al*, 2008; Trepel *et al*, 2005). Investigation of the relationship between the dopamine system and prospect theory seems promising, considering the fact that dopamine is linked to risk-seeking behavior (Leyton *et al*, 2002) and is involved in disrupted decision making observed in neuropsychiatric disorders such as drug/gambling addiction and Parkinson's disease (Steeves *et al*, 2009; Zack and Poulos, 2004). Based on the circumstantial findings, Trepel *et al* (2005) speculated in a thoughtful review that dopamine transmission in the striatum might be involved in shaping probability weighting. To test this speculation, 18 healthy male subjects were studied for D1 receptors with [^{11}C]SCH23390 PET, and 18 other healthy male subjects were studied for striatal D2 receptors with [^{11}C]raclopride PET (Takahashi *et al*, 2010*a*). To estimate decision weight, certainty equivalents were determined outside the PET scanner, based on the staircase procedure suggested by Tversky and Kahneman (1992). A gamble's certainty equivalent is the amount of sure payoff at which a player is indifferent between the sure payoff and the gamble. Participants were presented with options between a gamble and a sure payoff on a computer monitor. Gambles were presented that had an objective probability P of paying a known outcome x (and paying zero otherwise). Multiple gambles with different combinations of P and x were used. In each trial, the participants chose between a gamble and a sure payoff according to their preferences. Each time a choice was made between a gamble and a sure payoff in a trial, the amount of a sure payoff in the next trial was adjusted and eight trials per each gamble were

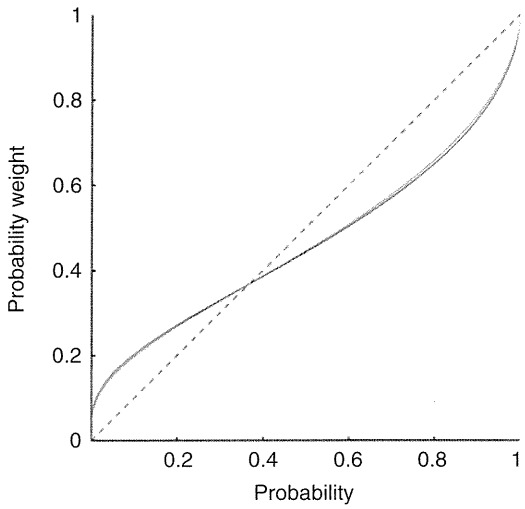

Figure 3 Average fitted probability-weighting function. Red line represents the first group with D1 receptors investigated, and black line the second group with striatal D2 receptors investigated.

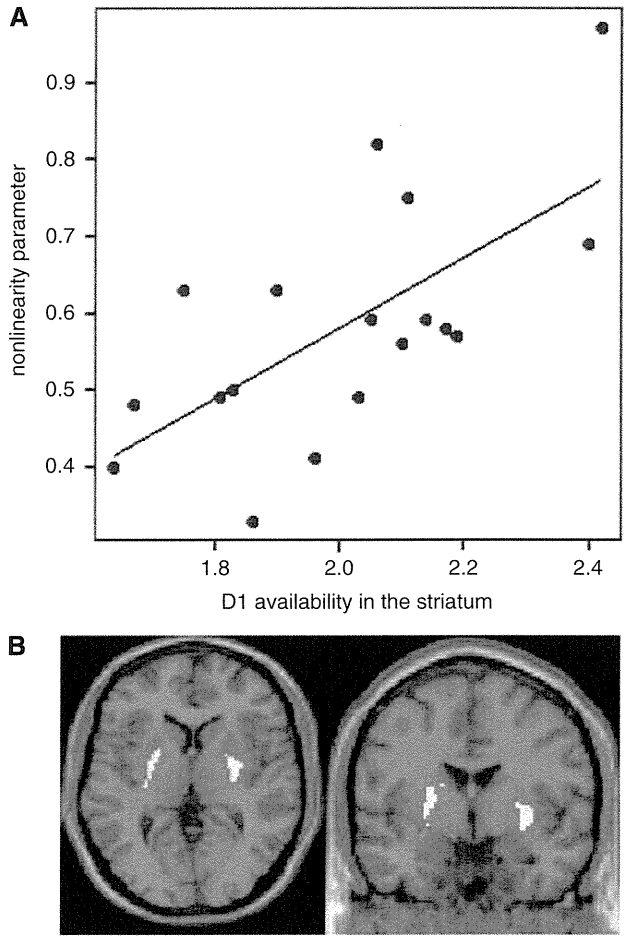

Figure 4 Correlation between nonlinearity of probabilities weighting and D1 receptor availability in the striatum. (**A**) Plots and regression line of correlation between α (nonlinearity parameter) and D1 receptor availability in the putamen ($r = 0.66$, $P = 0.003$). (**B**) Image showing regions of correlation between nonlinearity parameter of weighting function and D1 receptor availability in the striatum.

iterated to successively narrow the range including the certainty equivalents. On the basis of this certainty equivalents estimation experiment, we estimated probability weighting using the one-parameter function derived axiomatically by Prelec (1998), $w(p) = \exp\{-(\ln(1/p))^{\alpha}\}$ with $0 < \alpha < 1$. This $w(p)$ function has an inverted S-shape with a fixed inflection point at $p = 1/e = 0.37$ (at that point the probability $1/e$ also receives decision weight $1/e$). Nonlinearity is fully captured by a single parameter α. A smaller value of α (closer to 0) means a more nonlinear inflected weighting function and a higher value (closer to 1) means a more linear weighting function. At $\alpha = 1$, the function is linear.

In the first group, with D1 receptors investigated, mean (s.d.) α of the weighting function was 0.58 (0.16). In the second group, with striatal D2 receptors investigated, mean (s.d.) α was 0.56 (0.19), indicating that the two groups were comparable. Averaged weighting functions of the two groups are shown in Figure 3 (Takahashi *et al*, 2010*a*). Both regions of interest and voxel-by-voxel statistical parametric mapping analyses revealed significant positive correlation between striatal D1 receptor availability and the nonlinearity parameter α of weighting function (Figures 4A and 4B; Takahashi *et al*, 2010*a*). That is, people with lower striatal D1 receptor availability tend to show more pronounced overestimation of low probabilities and underestimation of high probabilities. It has been suggested that emotional responses to gambles influence weighting. In particular, the overweighting of low-probability gains may reflect hope of winning and the underweighting of high-probability gains may reflect fear of losing a 'near sure thing' (Trepel *et al*, 2005). One study supportive of this hypothesis found more nonlinear weighting functions for gambles over emotional outcomes (kisses and shocks) than over money (Rottenstreich and Hsee, 2001). In this sense, individuals with lower striatal D1 receptor availability might be interpreted as showing more 'emotional' decision making.

A neuroeconomics fMRI, using a simpler exposure-choice paradigm, showed that Prelec's nonlinearity parameter α was negatively correlated with striatal activity during reward anticipation under risk (Hsu *et al*, 2009). That is, people with a greater degree of nonlinearity in striatal activation to anticipated reward tend to overestimate low probabilities (to be risk seeking) and underestimate high probabilities (to be risk averse). Although the mechanism(s) linking the fMRI finding to our PET finding needs to be clarified in future investigations, our molecular imaging approach allows us to broaden our understanding of the neurobiological mechanism underlying decision making under risk beyond the knowledge attained by neuroeconomics fMRI.

Functional significance of individual difference in D1 receptors

All of our three studies mentioned above showed that individual differences in D1 receptor availability in the brain predicted the individual differences in brain functions (working memory/set shifting, emotional reaction, and decision making under risk) better than that of D2 receptor availability (Takahashi *et al*, 2008, 2010*a*,*b*). We do not think that dopamine D2 receptors have minimal roles in these brain functions. However, can we learn something from these studies showing the predominance of D1 receptors in terms of predicting these brain functions?

Dopamine neurons are known to show tonic firing and phasic (burst) firing, and in turn tonic and phasic dopamine release are induced, respectively (Grace, 1991; Grace *et al*, 2007). Phasic dopamine release in the striatum occurs during reward and reward-predicting stimuli (Grace, 1991; Schultz, 2007*b*). Phasic dopamine release in the amygdala is also induced in response to stress or emotional stimuli (Inglis and Moghaddam, 1999). Although both tonic and phasic dopamine release are necessary for PFC functions, phasic dopamine release has a crucial role in working memory and set shifting (Braver *et al*, 1999; Phillips *et al*, 2004). Thus, phasic dopamine release seems to be important for the brain functions that we investigated (working memory/set shifting, emotional reaction, and decision making under risk).

It has been shown that D1 receptors have much less affinity to endogenous dopamine than D2 receptors (Richfield *et al*, 1989). Furthermore, cortical and striatal D1 receptors are known to be predominantly extrasynaptic (Caille *et al*, 1996; Smiley *et al*, 1994). These facts suggest that D1-mediated neurotransmission is mainly governed by volume transmission (Dreher and Burnod, 2002; Garris *et al*, 1994), which might be induced by the phasic dopamine release from axonal terminals (Schultz, 2007*a*). Therefore, it can be suggested that available D1 receptors are preferentially stimulated by phasically released DA, whereas low-level baseline tonic dopamine release is sufficient for stimulating D2 receptors (Frank *et al*, 2007; Schultz, 2007*b*). A recent computational model also showed that phasic dopamine release primarily increases D1 occupancy, whereas D2 occupancy was less affected (Dreyer *et al*, 2010). Thus, these considerations lead us to believe that the variability of available D1 receptors might be more associated with individual differences in brain functions that require phasic dopamine release.

Clinical implications

Our previous PET study using [^{11}C]SCH23390 revealed that, compared with normal controls, D1 receptors in PFC were decreased in schizophrenia, which was associated with poor performance on WCST (Okubo *et al*, 1997*b*). However, another PET study using [^{11}C]NNC112 reported that increased D1 receptors in PFC were associated with working memory deficits in schizophrenia (Abi-Dargham *et al*, 2002). The same research group recently replicated increased D1 receptors in PFC of drug-naive schizophrenia patients (Abi-Dargham *et al*, 2011). The group also reported that PFC D1 receptor availability measured by [^{11}C]NNC112 was significantly upregulated in chronic ketamine users, although no significant relationships were found between PFC D1 receptor availability and performance on working memory tests (Narendran *et al*, 2005).

It has been discussed that these inconsistent results might stem from several factors including differences in radioligands, but our more recent PET study measuring cortical D1 receptors with both [^{11}C]SCH23390 and [^{11}C]NNC112 in the same schizophrenia population showed that prefrontal D1 receptors were decreased in chronic schizophrenia regardless of radioligands (Kosaka *et al*, 2010). Still, the reasons for these inconsistent results need to be clarified in the future. An inverted U-shaped response might account for working memory deficits in schizophrenia patients, whether D1 receptors in PFC are increased or decreased in patients.

The central profile of most antipsychotics is the D2 receptor blockade property. Antipsychotics are reasonably effective in ameliorating positive symptoms in schizophrenia. However, negative symptoms and cognitive impairments of schizophrenia are typically not responsive to antipsychotic therapy. This has led to the investigation of alternative agents for the treatment of cognitive impairments in schizophrenia, and a body of data from animal and human studies support the utility of the D1 agonist (Buchanan *et al*, 2007; Okubo *et al*, 1997*a*). However, the efficacy of D1 agonists on cognitive impairments has not so far been proven due to several practical issues of drug development. In addition to these issues, we need to taken into account the fact that schizophrenia is a heterogeneous disorder. D1 receptor density might be different according to the type of the disease, changeable even in a single patient according to its stage (prodromal phase, first episode phase, and chronic phase). The inverted U-shaped property of D1 receptor stimulation might lead to bidirectional effect of D1 agonist depending on the type or stage of schizophrenia. Anhedonia or blunted affect is one of the central features of negative symptoms. Some neuroimaging studies have suggested that reduced amygdala activation was associated with these symptoms (Dowd and Barch, 2010; Takahashi *et al*, 2004). Therefore, similarly to the strategy for cognitive impairment, D1 agonist might be useful for restoring amygdala activation, and consequently improve these negative symptoms.

Misestimating risk could lead to disadvantaged choices such as initiation of drug use/gambling and transition to regular drug use/gambling (Kreek *et al*, 2005). Our studies have shown that people with lower striatal D1 receptor availability tend to misestimate the weight of probabilities, and in particular, to overestimate low probabilities of winning gambles (risk seeking). This finding led us to the intuitive conjecture that D1 agonist, again, might be useful for easing misestimation of risk, and consequently beneficial for pathological gambling. However, on the contrary, clinical reports have indicated the association between dopamine agonist medication and the emergence of pathological gambling in Parkinson's disease patients (Gallagher *et al*, 2007). Although early reports implicated D3 receptor agonists as being most likely to induce pathological gambling in Parkinson's disease patients (Dodd *et al*, 2005), it has been reported that mixed D1/D2 receptor agonists can also promote pathological gambling (Lu *et al*, 2006). These clinical findings appear to challenge our prediction, but indeed they may not. Pathological gambling is a complex behavior, which has been related to failures in impulse control or response inhibition as observed in Parkinson's disease, but also to impaired decision making, including risky or ambiguous decision. Estimation of risk requires the latter high-level processing, and we would argue that this is related to striatal D1 receptor availability, leading to the following hypothesis: low-level striatal D1 receptor availability (which might in part be determined by genetic factors) is linked to a risk-seeking trait. The risk-seeking trait was reported to be linked to enhanced activation and DA release in the striatum during risk-seeking behavior (Leyton *et al*, 2002; St Onge and Floresco, 2009). Chronic exposure to unusually high release of DA by risk-seeking behavior might induce downregulation of D1 receptors (Moore *et al*, 1998; Yasuno *et al*, 2007). The further decrease in D1 receptor availability then leads to further risk seeking. Low-level striatal D1 receptor availability could therefore be a gateway to a vicious cycle, creating a predisposition to drug addiction and pathological gambling. Recently, circumstantial evidence to support this hypothesis has been reported. Martinez *et al* (2009), based on their PET study, suggested that reduced D1 receptor binding may be associated with an increased risk of relapse in cocaine addiction. Needless to say, this tentative hypothesis needs to be tested in future investigations, and we believe that understanding the molecular mechanism of extreme or impaired decision making will contribute to the assessment and prevention of drug and gambling addiction as well as the development of novel pharmacological therapies for these addictions. In conclusion, interdisciplinary approach combining molecular imaging techniques with cognitive neuroscience and clinical psychiatry will provide new perspectives for understanding the neurobiology of neuropsychiatric disorders and their innovative drug developments.

Acknowledgements

A part of this study is the result of 'Integrated research on neuropsychiatric disorders' carried out under the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science, and Technology of Japan (MEXT), a Grant-in-aid for scientific research on innovative areas: Prediction and Decision Making (23120009), a Grant by Takeda Science Foundation and a consignment expense for the Molecular Imaging Program on 'Research Base for PET Diagnosis' from MEXT.

Disclosure/conflict of interest

The authors declare no conflict of interest.

References

Aalto S, Bruck A, Laine M, Nagren K, Rinne JO (2005) Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [11C]FLB 457. *J Neurosci* 25:2471–7

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M (2002) Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 22:3708–19

Abi-Dargham A, Xu X, Thompson JL, Gil R, Kegeles LS, Urban NB, Narendran R, Hwang DR, Laruelle M, Slifstein M (2011) Increased prefrontal cortical D1 receptors in drug naive patients with schizophrenia: a PET study with [11C]NNC112. *J Psychopharmacol*; Epub ahead of print

Asan E (1998) The catecholaminergic innervation of the rat amygdala. *Adv Anat Embryol Cell Biol* 142:1–118

Bäckman L, Karlsson S, Fischer H, Karlsson P, Brehmer Y, Rieckmann A, MacDonald SW, Farde L, Nyberg L (2011) Dopamine D(1) receptors and age differences in brain activation during working memory. *Neurobiol Aging* 32:1849–56

Bissiere S, Humeau Y, Luthi A (2003) Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition. *Nat Neurosci* 6:587–92

Braver TS, Barch DM, Cohen JD (1999) Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. *Biol Psychiatry* 46:312–28

Buchanan RW, Freedman R, Javitt DC, Abi-Dargham A, Lieberman JA (2007) Recent advances in the development of novel pharmacological agents for the treatment of cognitive impairments in schizophrenia. *Schizophr Bull* 33:1120–30

Caille I, Dumartin B, Bloch B (1996) Ultrastructural localization of D1 dopamine receptor immunoreactivity in rat striatonigral neurons and its relation with dopaminergic innervation. *Brain Res* 730:17–31

Camerer C, Loewenstein G (2004) Behavioral economics: past, present, future. In: *Advance in behavioral economics* (Camerer C, Loewenstein G, Rabin M, eds), Princeton, NJ: Princeton University Press pp 3–51

Castner SA, Goldman-Rakic PS (2004) Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D1 receptor stimulation. *J Neurosci* 24:1446–50

Cools R, D'Esposito M (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry* 69:113–25

Corkin S (2001) Beware of frontal lobe deficits in hippocampal clothing. *Trends Cogn Sci* 5:321–3

de la Mora MP, Gallegos-Cari A, Arizmendi-Garcia Y, Marcellino D, Fuxe K (2010) Role of dopamine receptor mechanisms in the amygdaloid modulation of fear and anxiety: structural and functional analysis. *Prog Neurobiol* 90:198–216

De Martino B, Kumaran D, Seymour B, Dolan RJ (2006) Frames, biases, and rational decision-making in the human brain. *Science* 313:684–7

Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE (2005) Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 62:1377–81

Dowd EC, Barch DM (2010) Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. *Biol Psychiatry* 67:902–11

Dreher JC, Burnod Y (2002) An integrative theory of the phasic and tonic modes of dopamine modulation in the prefrontal cortex. *Neural Netw* 15:583–602

Dreyer JK, Herrik KF, Berg RW, Hounsgaard JD (2010) Influence of phasic and tonic dopamine release on receptor activation. *J Neurosci* 30:14273–83

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci USA* 98:6917–22

Ekelund J, Slifstein M, Narendran R, Guillin O, Belani H, Guo N, Hwang Y, Hwang D, Abi-Dargham A, Laruelle M (2007) *In vivo* DA D 1 receptor selectivity of NNC 112 and SCH 23390. *Mol Imaging Biol* 9:117–25

Floresco SB, Magyar O (2006) Mesocortical dopamine modulation of executive functions: beyond working memory. *Psychopharmacology (Berl)* 188:567–85

Fox C, Poldrack R (2009) Prospect theory and the brain. In: *Neuroeconomics* (Glimcher PW, Camerer C, Fehr E, Poldrack R, eds), London: Academic Press pp 145–74

Frank M, Scheres A, Sherman S (2007) Understanding decision-making deficits in neurological conditions: insights from models of natural action selection. *Philos Trans R Soc London B Biol Sci* 362:1641–54

Gallagher DA, O'Sullivan SS, Evans AH, Lees AJ, Schrag A (2007) Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. *Mov Disord* 22:1757–63

Garris PA, Ciolkowski EL, Pastore P, Wightman R (1994) Efflux of dopamine from the synaptic cleft in the nucleus accumbens of the rat brain. *J Neurosci* 14: 6084–93

Glickstein SB, Hof PR, Schmauss C (2002) Mice lacking dopamine D2 and D3 receptors have spatial working memory deficits. *J Neurosci* 22:5619–29

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR (2003) Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry* 60:889–96

Goldman-Rakic PS, Muly III EC, Williams GV (2000) D(1) receptors in prefrontal cells and circuits. *Brain Res Brain Res Rev* 31:295–301

Goto Y, Grace AA (2008) Dopamine modulation of hippocampal prefrontal cortical interaction drives memory-guided behavior. *Cereb Cortex* 18:1407–14

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 41:1–24

Grace AA, Floresco SB, Goto Y, Lodge DJ (2007) Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends Neurosci* 30:220–7

Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994) Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology* 11:245–56

Hariri AR, Mattay VS, Tessitore A, Fera F, Smith WG, Weinberger DR (2002) Dextroamphetamine modulates the response of the human amygdala. *Neuropsychopharmacology* 27:1036–40

Hsu M, Krajbich I, Zhao C, Camerer C (2009) Neural response to reward anticipation under risk is nonlinear in probabilities. *J Neurosci* 29:2231

Igarashi K, Oguni H, Osawa M, Awaya Y, Kato M, Mimura M, Kashima H (2002) Wisconsin card sorting test in children with temporal lobe epilepsy. *Brain Dev* 24: 174–8

Inglis FM, Moghaddam B (1999) Dopaminergic innervation of the amygdala is highly responsive to stress. *J Neurochem* 72:1088–94

Ito H, Takahashi H, Arakawa R, Takano H, Suhara T (2008) Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. *Neuroimage* 39:555–65

Kienast T, Hariri AR, Schlagenhauf F, Wrase J, Sterzer P, Buchholz HG, Smolka MN, Grunder G, Cumming P, Kumakura Y, Bartenstein P, Dolan RJ, Heinz A (2008) Dopamine in amygdala gates limbic processing of aversive stimuli in humans. *Nat Neurosci* 11:1381–2

Kosaka J, Takahashi H, Ito H, Takano A, Fujimura Y, Matsumoto R, Nozaki S, Yasuno F, Okubo Y, Kishimoto T, Suhata T (2010) Decreased binding of [11C] NNC112 and [11C] SCH23390 in patients with chronic schizophrenia. *Life Sci* 86:814–8

Kreek MJ, Nielsen DA, Butelman ER, LaForge KS (2005) Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nat Neurosci* 8:1450–7

Kroner S, Rosenkranz JA, Grace AA, Barrionuevo G (2005) Dopamine modulates excitability of basolateral amygdala neurons *in vitro*. *J Neurophysiol* 93:1598–610

Laroche S, Davis S, Jay TM (2000) Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. *Hippocampus* 10:438–46

LeDoux JE (2000) Emotion circuits in the brain. *Annu Rev Neurosci* 23:155–84

Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A (2002) Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C] raclopride study in healthy men. *Neuropsychopharmacology* 27:1027

Lidow MS, Koh PO, Arnsten AF (2003) D1 dopamine receptors in the mouse prefrontal cortex: immunocytochemical and cognitive neuropharmacological analyses. *Synapse* 47:101–8

Lu C, Bharmal A, Suchowersky O (2006) Gambling and Parkinson disease. *Arch Neurol* 63:298

MacDonald SW, Cervenka S, Farde L, Nyberg L, Backman L (2009) Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning. *Neuropsychologia* 47:2299–304

Marowsky A, Yanagawa Y, Obata K, Vogt KE (2005) A specialized subclass of interneurons mediates dopaminergic facilitation of amygdala function. *Neuron* 48:1025–37

Martinez D, Slifstein M, Narendran R, Foltin RW, Broft A, Hwang DR, Perez A, Abi-Dargham A, Fischman MW, Kleber HD, Laruelle M (2009) Dopamine D1 receptors in cocaine dependence measured with PET and the choice to self-administer cocaine. *Neuropsychopharmacology* 34:1774–82

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci USA* 100: 6186–91

McDowell S, Whyte J, D'Esposito M (1998) Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. *Brain* 121:1155–64

McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H, Klingberg T (2009) Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science* 323:800–2

Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW (1999) Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacology (Berl)* 146:162–74

Moore R, Vinsant S, Nader M, Porrino L, Friedman D (1998) Effect of cocaine self-administration on dopamine D2 receptors in rhesus monkeys. *Synapse* 30:88–96

Müller U, von Cramon DY, Pollmann S (1998) D1- versus D2-receptor modulation of visuospatial working memory in humans. *J Neurosci* 18:2720–8

Narendran R, Frankle WG, Keefe R, Gil R, Martinez D, Slifstein M, Kegeles LS, Talbot PS, Huang Y, Hwang DR, Khenissi L, Cooper TB, Laruelle M, Abi-Dargham A (2005) Altered prefrontal dopaminergic function in chronic recreational ketamine users. *Am J Psychiatry* 162:2352–9

Okubo Y, Suhara T, Sudo Y, Toru M (1997*a*) Possible role of dopamine D1 receptors in schizophrenia. *Mol Psychiatry* 2:291–2

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M (1997*b*) Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* 385:634–6

Pezze MA, Feldon J (2004) Mesolimbic dopaminergic pathways in fear conditioning. *Prog Neurobiol* 74: 301–20

Phillips AG, Ahn S, Floresco SB (2004) Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. *J Neurosci* 24:547–53

Prelec D (1998) The probability weighting function. *Econometrica* 66:497–527

Rangel A, Camerer C, Montague PR (2008) A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* 9:545–56

Richfield EK, Penney JB, Young AB (1989) Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. *Neuroscience* 30:767–77

Rosenkranz JA, Grace AA (1999) Modulation of basolateral amygdala neuronal firing and afferent drive by dopamine receptor activation *in vivo*. *J Neurosci* 19:11027–39

Rosenkranz JA, Grace AA (2002) Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons *in vivo*. *J Neurosci* 22:324–37

Rottenstreich Y, Hsee CK (2001) Money, kisses, and electric shocks: on the affective psychology of risk. *Psychol Sci* 12:185–90

Royer S, Martina M, Pare D (1999) An inhibitory interface gates impulse traffic between the input and output stations of the amygdala. *J Neurosci* 19:10575–83

Sawaguchi T, Goldman-Rakic PS (1994) The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J Neurophysiol* 71:515–28

Schultz W (2007*a*) Multiple dopamine functions at different time courses. *Annu Rev Neurosci* 30:259–88

Schultz W (2007*b*) Behavioral dopamine signals. *Trends Neurosci* 30:203–10

Seamans JK, Floresco SB, Phillips AG (1998) D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. *J Neurosci* 18:1613–21

Seamans JK, Yang CR (2004) The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog Neurobiol* 74:1–58

Slifstein M, Kegeles LS, Gonzales R, Frankle WG, Xu X, Laruelle M, Abi-Dargham A (2007) [11C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT(2A) receptors: a PET study in healthy human subjects. *J Cereb Blood Flow Metab* 27:1733–41

Slifstein M, Kolachana B, Simpson EH, Tabares P, Cheng B, Duvall M, Frankle WG, Weinberger DR, Laruelle M, Abi-Dargham A (2008) COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C]NNC112 and PET. *Mol Psychiatry* 13:821–7

Smiley JF, Levey AI, Ciliax BJ, Goldman-Rakic PS (1994) D1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: predominant and extrasynaptic localization in dendritic spines. *Proc Natl Acad Sci USA* 91:5720–4

Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, Rusjan P, Houle S, Strafella AP (2009) Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain* 132:1376–85

St Onge JR, Floresco SB (2009) Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology* 34:681–97

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

Takahashi H, Kato M, Hayashi M, Okubo Y, Takano A, Ito H, Suhara T (2007) Memory and frontal lobe functions; possible relations with dopamine D2 receptors in the hippocampus. *Neuroimage* 34:1643–9

Takahashi H, Kato M, Takano H, Arakawa R, Okumura M, Otsuka T, Kodaka F, Hayashi M, Okubo Y, Ito H, Suhara

T (2008) Differential contributions of prefrontal and hippocampal dopamine D(1) and D(2) receptors in human cognitive functions. *J Neurosci* 28:12032–8

Takahashi H, Koeda M, Oda K, Matsuda T, Matsushima E, Matsuura M, Asai K, Okubo Y (2004) An fMRI study of differential neural response to affective pictures in schizophrenia. *Neuroimage* 22:1247–54

Takahashi H, Matsui H, Camerer C, Takano H, Kodaka F, Ideno T, Okubo S, Takemura K, Arakawa R, Eguchi Y, Murai T, Okubo Y, Kato M, Ito H, Suhara T (2010*a*) Dopamine D receptors and nonlinear probability weighting in risky choice. *J Neurosci* 30:16567–72

Takahashi H, Takano H, Kodaka F, Arakawa R, Yamada M, Otsuka T, Hirano Y, Kikyo H, Okubo Y, Kato M, Obata T, Ito H, Suhara T (2010*b*) Contribution of dopamine D1 and D2 receptors to amygdala activity in human. *J Neurosci* 30:3043–7

Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, Okubo Y (2005) Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. *Neuroimage* 27:991–1001

Tessitore A, Hariri AR, Fera F, Smith WG, Chase TN, Hyde TM, Weinberger DR, Mattay VS (2002) Dopamine modulates the response of the human amygdala: a study in Parkinson's disease. *J Neurosci* 22:9099–103

Thierry AM, Gioanni Y, Degenetais E, Glowinski J (2000) Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. *Hippocampus* 10:411–9

Tom S, Fox C, Trepel C, Poldrack R (2007) The neural basis of loss aversion in decision-making under risk. *Science* 315:515

Trepel C, Fox C, Poldrack R (2005) Prospect theory on the brain? Toward a cognitive neuroscience of decision under risk. *Cogn Brain Res* 23:34–50

Tseng KY, Lewis BL, Lipska BK, O'Donnell P (2007) Post-pubertal disruption of medial prefrontal cortical dopamine-glutamate interactions in a developmental animal model of schizophrenia. *Biol Psychiatry* 62:730–8

Tversky A, Kahneman D (1992) Advances in prospect theory: cumulative representation of uncertainty. *J Risk Uncertain* 5:297–323

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF (2007) Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat Neurosci* 10:376–84

Williams GV, Castner SA (2006) Under the curve: critical issues for elucidating D1 receptor function in working memory. *Neuroscience* 139:263–76

Williams-Gray CH, Hampshire A, Robbins TW, Owen AM, Barker RA (2007) Catechol O-methyltransferase Val158-Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. *J Neurosci* 27:4832–8

Yamamoto R, Ueta Y, Kato N (2007) Dopamine induces a slow after depolarization in lateral amygdala neurons. *J Neurophysiol* 98:984–92

Yasuno F, Ota M, Ando K, Ando T, Maeda J, Ichimiya T, Takano A, Doronbekov TK, Fujimura Y, Nozaki S, Suhara T (2007) Role of ventral striatal dopamine D1 receptor in cigarette craving. *Biol Psychiatry* 61:1252–9

Zack M, Poulos C (2004) Amphetamine primes motivation to gamble and gambling-related semantic networks in problem gamblers. *Neuropsychopharmacology* 29:195–207

Molecular Psychiatry (2012), 1–2

www.nature.com/mp

LETTER TO THE EDITOR

Norepinephrine in the brain is associated with aversion to financial loss

Molecular Psychiatry advance online publication, 21 February 2012; doi:10.1038/mp.2012.7

Understanding the molecular mechanism of extreme or impaired decision-making observed in neuropsychiatric disorders, such as pathological gambling and attention-deficit hyperactivity disorder (ADHD), could contribute to better assessment and the development of novel pharmacological therapies for those disorders. Typically, most people show a disproportionate distaste for possible losses compared with equal-sized gains. This human *in vivo* molecular imaging study has demonstrated that individuals with lower thalamic norepinephrine transporters (NET) showed more exaggerated aversion to financial loss.

Empirical and field studies suggest that losses have greater impact than equivalent gains.[1] For example, a typical person would only accept a two-outcome gamble in which $50 could be lost if the possible gain is $100, twice as large. This greater sensitivity to losses than to gains is called 'loss aversion' and substantial individual differences in it have been observed in many behavioral studies.[1,2] In psychiatric populations, pathological gambling showed diminished sensitivity to monetary loss itself and, more specifically, patients with ADHD and psychopaths showed reduced sensitivity to the magnitude of monetary loss.[3,4]

Recent functional magnetic resonance imaging and lesion studies have shown that the prefrontal cortex (PFC), striatum and amygdala are involved in loss aversion.[5,6] However, little is known about modulatory neurotransmission in this phenomenon. There is circumstantial evidence that NE may be important for loss aversion. Central NE blockade by propranolol reduced sensitivity to the magnitude of possible losses from gambles.[7] A recent psychophysiological study demonstrated that arousal is associated with loss aversion.[8] We utilized positron emission tomography (PET) scans with (S,S)-[^{18}F]FMeNER-D$_2$ to investigate the relationship between central NET and loss aversion. A NET-rich region available to PET imaging with this ligand is the thalamus. The amygdala and PFC are also innervated by NE, but relatively low expression of NET prevented reliable measurement of their NET binding in the current study. We expected that NET in the thalamus would mediate loss aversion.

In all, 19 healthy male volunteers participated in PET scans for quantification of NET in the brain. Brain radioactivities were measured with scanning from 0 to 90 min, followed by scanning from 120 to 180 min. The region-of-interest was set on the bilateral thalamus. NET binding in the thalamus was calculated by the area-under-the-curve ratio method using the PMOD software package (PMOD Technologies, Zurich, Switzerland). An integration interval of 120–180 min was used in this method because specific binding reaches a peak during this period of PET measurement (Supplementary Information). Loss aversion parameters were determined outside the PET scanner. Participants were presented mixed gambles that had a 50% chance of losing a fixed amount of X and a 50% chance of gaining Y. The amounts of possible gain Y to make up for a 50% chance of losing X were determined by a staircase procedure (Supplementary Information), yielding an estimate of loss aversion λ from $Y=\lambda \times X$. A median of λ was 3.01 (range: 0.98–9.98). Mean binding potential of (S,S)-[^{18}F]FMeNER-D$_2$ in the thalamus was 0.57 ± 0.10. There was a strong negative correlation between λ and NET binding in the thalamus (Figure 1).

Although NE has been implicated in arousal, recent studies also suggest that NE affects processing of salient information.[9] Neurons of the locus coeruleus (LC), the major source of NE in the brain, is phasically evoked by salient or emotional stimuli, and phasic LC activation also increases NE release in target sites.[9] Increasing NE tone by NE reuptake inhibitor improves detection of emotional stimuli,[10] and blockade of central NE by propranolol attenuates the sensitivity to the magnitude of possible losses.[7]

A recent study showed that, on average, physiological arousal response to losses was greater than to equivalent gains.[8] This means that losses are more emotionally laden and salient than equivalent gains. The study also reported that individuals with greater arousal response to losses versus gains tend to be more loss aversive.[8] Thus, our finding suggests that individuals with low NET might show an enhanced effect of NE released by salient stimuli due to low re-uptake, and consequently show pronounced emotional or arousal response to losses relative to gains. Due to radioligand limitations, we could not test the amygdala and PFC, which are innervated by NE and implicated in loss aversion. Thalamic NET might be an indirect mediator of the relationship between NE transmission and loss aversion. It stands to reason that careful interpretation is needed, and future investigation will be required. In any event, we believe that this novel finding could provide new

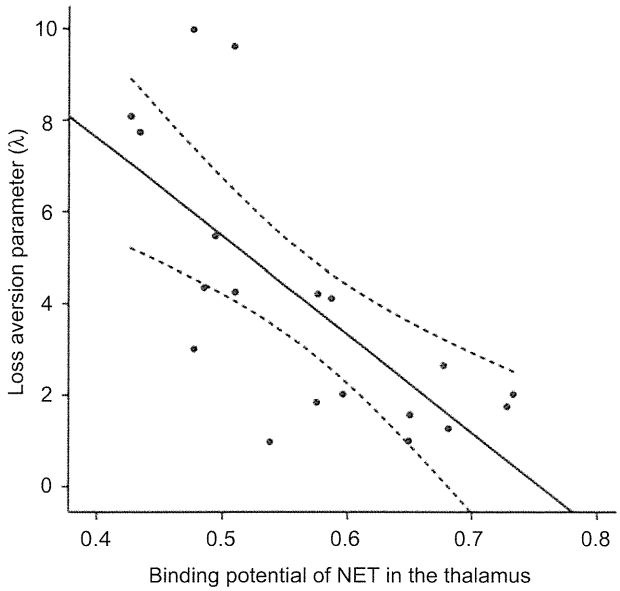

Figure 1 Correlation between loss aversion parameters and norepinephrine transporters (NET) binding in the thalamus. Plots and regression line of correlation between λ and Binding potential of the thalamus ($R = -0.71$, $P < 0.001$). The dashed lines are 95% confidence interval boundaries.

perspectives on altered decision making observed in neuropsychiatric disorders.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

A part of this study is the result of 'Integrated research on neuropsychiatric disorders' carried out under the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT). This work was supported by Grants-in-aid for Scientific Research (23120009, 23680045), Takeda Science Foundation and Casio Science Foundation.

H Takahashi[1,2,3,4], S Fujie[2], C Camerer[5], R Arakawa[2], H Takano[2], F Kodaka[2], H Matsui[2], T Ideno[6], S Okubo[6], K Takemura[6], M Yamada[2,3], Y Eguchi[2], T Murai[1], Y Okubo[7], M Kato[8], H Ito[2] and T Suhara[2]
[1]*Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, Japan;* [2]*Molecular Imaging Center, Department of Molecular Neuroimaging, National Institute of Radiological Sciences, Chiba, Japan;* [3]*Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Saitama, Japan;* [4]*Brain Science Institute, Tamagawa University, Tokyo, Japan;* [5]*Division of Humanities and Social Sciences, California Institute of Technology, Pasadena, CA, USA;* [6]*Department of Psychology, Waseda University, Tokyo, Japan;* [7]*Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan and* [8]*Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan*
E-mail: hidehiko@kuhp.kyoto-u.ac.jp

References

1 Camerer C, Loewenstein G. In: Camerer C, Loewenstein G, Rabin M (eds). *Advance in Behavioral Economics*. Princeton University Press: Princeton, 2004, pp 3–51.
2 Abdellaoui M, Bleichrodt H, Paraschiv C. *Manage Sci* 2007; **53**: 1659–1674.
3 Blair K, Morton J, Leonardand A, Blair RJR. *Pers Individ Dif* 2006; **41**: 155–165.
4 Van Holst RJ, Van Den Brink W, Veltman DJ, Goudriaan AE. *Neurosci Biobehav Rev* 2010; **34**: 87–107.
5 Tom S, Fox C, Trepel C, Poldrack R. *Science* 2007; **315**: 515–518.
6 De Martino B, Camerer CF, Adolphs R. *Proc Natl Acad Sci USA* 2010; **107**: 3788–3792.
7 Rogers RD, Lancaster M, Wakeley J, Bhagwagar Z. *Psychopharmacology* 2004; **172**: 157–164.
8 Sokol-Hessner P, Hsu M, Curley NG, Delgado MR, Camerer CF, Phelps EA. *Proc Natl Acad Sci USA* 2009; **106**: 5035–5040.
9 Berridge CW. *Brain Res Rev* 2008; **58**: 1–17.
10 De Martino B, Strange BA, Dolan RJ. *Psychopharmacology* 2008; **197**: 127–136.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

NeuroImage 56 (2011) 1105–1110

Contents lists available at ScienceDirect

NeuroImage

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

Effect of radiolabeled metabolite elimination from the brain on the accuracy of cerebral enzyme activity estimation using positron emission tomography with substrate tracers

Tomoyuki Ohya [a], Toshimitsu Okamura [a], Yuji Nagai [b], Kiyoshi Fukushi [a], Toshiaki Irie [a], Tetsuya Suhara [b], Ming-Rong Zhang [a], Toshimitsu Fukumura [a], Tatsuya Kikuchi [a,*]

[a] Molecular Probe Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan
[b] Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan

ARTICLE INFO

Article history:
Received 4 November 2010
Revised 27 January 2011
Accepted 9 February 2011
Available online 13 February 2011

Keywords:
Positron emission tomography
Brain
Enzyme
Metabolite elimination
Tracer kinetics
Tracer sensitivity

ABSTRACT

Cerebral enzyme activity can be quantified using positron emission tomography (PET) in conjunction with a radiolabeled enzyme substrate. We investigated the relationship between the elimination rate (k_{el}) of tracer metabolites from the brain and the precision of target enzyme activity estimation (k_3). An initial simulation study indicated that the precision of k_3 estimates was highly dependent on k_{el}, and was characterized by several kinetic parameters including the ratio of k_{el} and the efflux rate (k_2) of authentic tracer ($\beta \equiv k_{el}/k_2$). The optimal tracer condition for high sensitivity was found to be $\beta < 0.1$. To verify the simulation results, we performed a PET study with a single monkey using two PET tracers, *N*-[^{18}F]fluoroethylpiperidin-4-ylmethyl acetate ([^{18}F]FEP-4MA) and *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A). Both of these substrate type tracers were developed for measuring cerebral acetylcholinesterase activity. There was good retention of the radioactive metabolite of [^{11}C]MP4A in the brain ($k_{el} = 0.0036 \pm 0.0013$ min^{-1}, $\beta = 0.028$), whereas that of [^{18}F]FEP-4MA was eliminated from the brain ($k_{el} = 0.012 \pm 0.0010$ min^{-1}, $\beta = 0.085$). A non-linear least square analysis for simultaneous estimation of all parameters showed that the precision of the k_3 estimate for [^{18}F]FEP-4MA was as high (7.4%) as that for [^{11}C]MP4A (10%). These results indicate that tracers with metabolites that are eliminated from the brain at a slow rate ($\beta < 0.1$) may be useful for the quantitative measurement of target enzyme activity.

Introduction

Cerebral enzyme activity can be quantified using positron emission tomography (PET) in conjunction with a radio-labeled enzyme substrate. Fig. 1 depicts a postulated compartmental model of a tracer based on the rationale of enzyme-mediated trapping. In this model, k_3 represents the enzyme-mediated first-order metabolic rate of the tracer, and can be estimated by kinetic analysis of the time activity curve (TAC) in the brain, as measured with PET. *N*-[^{11}C] Methylpiperidin-4-yl acetate ([^{11}C]MP4A), an acetylcholinesterase substrate, has been clinically used for the measurement of cerebral acetylcholinesterase activity based on this rationale (Shinotoh et al., 2004).

An effective tracer based on radioactive metabolite trapping must possess several properties, including a high specificity for the target enzyme, a moderate metabolic rate, and high blood brain barrier permeability. In terms of the second property, it has been reported that the ratio of the metabolic rate (k_3) and the efflux rate (k_2) of a given tracer, i.e. $\alpha \equiv k_3/k_2$ (the kinetic parameter proposed by Lassen et al., 1988), can affect the reliability of data in static and dynamic analysis (Fukushi et al., 1993; Koeppe et al., 1994, 1999). In terms of the third property, it is expected that a high blood brain barrier permeability of the tracer metabolite is not a desirable quality, unlike the case for the authentic tracer. The influx of metabolite into the brain makes it difficult to estimate k_3, and the elimination of metabolite from the brain would be expected to reduce the radioactivity in the brain. Thus, an effective radioactive metabolite should have hydrophilic properties to limit membrane permeability. However, even hydrophilic metabolites can be extruded from the brain by an efflux transporter. *N*-[^{11}C]Methylhalopurine derivatives, glutathione S-transferase substrates, are metabolized to form hydrophilic glutathione conjugates (Okamura et al., 2007, 2009). Glutathione conjugates are extruded from the brain by an efflux transporter, but they do not enter the brain from the blood. Similarly, the hydrophilic

Abbreviations: PET, positron emission tomography; TAC, time activity curve; MP4A, *N*-methylpiperidin-4-yl acetate; FEP-4MA, *N*-fluoroethylpiperidin-4-ylmethyl acetate; CV, coefficient of variation; NLS, non-linear least square; TLC, thin layer chromatography; PMP, *N*-methylpiperidin-4-yl propionate; %ID, percentage injected dose.

* Corresponding author at: National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. Fax: +81 43 206 3261.
E-mail address: kiku@nirs.go.jp (T. Kikuchi).

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.02.030

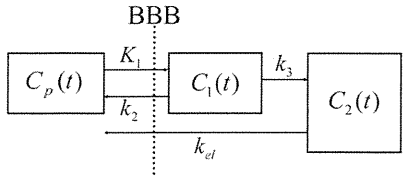

Fig. 1. Two-tissue compartment model with four parameters, for an incomplete trapping irreversible tracer. It can be seen that uptake of the metabolites of a given tracer from the arterial plasma to the brain cannot occur. C_1 and C_2 represent the concentration of the authentic and metabolized tracer in the brain, respectively. C_p represents the concentration of the authentic tracer in arterial plasma. K_1, k_2, k_3 and k_{el} represent the rate parameters in the model, corresponding to the influx rate constant, the efflux rate constant, the metabolic rate constant and the elimination rate constant, respectively.

metabolite of *N*-[^{18}F]fluoroethylpiperidin-4-ylmethyl acetate ([^{18}F]FEP-4MA), an acetylcholinesterase substrate, is extruded from the brain, but does not enter the brain from the blood (Kikuchi et al., 2010). In addition, the efflux rate of the [^{11}C]MP4A metabolites from the brain were low but not zero. However, it remains unclear how the extent of elimination of the tracer metabolites affects the sensitivity of a tracer for detecting changes in target enzyme activity (i.e. k_3 parameter changes).

In this study, we investigated the relationship between the kinetic properties of tracers in terms of the elimination of tracer metabolites, in addition to tracer α-value, and the precision of k_3 estimates using a simulation technique. In addition, we validated our simulation results with a dynamic PET experiment in a monkey using [^{11}C]MP4A and [^{18}F]FEP-4MA as model tracers.

Materials and methods

Theoretical basis

General

When the metabolites of a tracer in the blood do not enter the brain, in contrast to the elimination of the metabolite from the brain, the kinetics of such a tracer can be described by a two-tissue compartment model with four parameters (Friberg et al., 1994; Fig. 1). The time-course of the concentration of total radioactivity in the brain, which is the sum of authentic and metabolized tracer ($C_t = C_1 + C_2$), is expressed as:

$$C_t = K_1 \cdot e^{-(k_2+k_3)t} \otimes C_p + \frac{K_1 k_3}{k_2 + k_3 - k_{el}} \left(e^{-k_{el}t} - e^{-(k_2+k_3)t}\right) \otimes C_p \quad (1)$$

where K_1 represents the influx rate constant, k_2 represents the efflux rate constant, k_3 represents the metabolic rate constant, k_{el} represents the elimination rate constant of tracer metabolites, and C_p represents the concentration of an authentic tracer in arterial plasma.

β-value as kinetic parameter

It has been reported that the ratio of the metabolic rate constant (k_3) and efflux rate constant (k_2), i.e. α-value, determines the sensitivity of irreversible tracers (Koeppe et al., 1999). Besides the tracer α-value, we must consider the kinetic effects of metabolite elimination on tracer sensitivity, when the metabolite is eliminated from the brain. The Eq. (1) can be rewritten as follows:

$$C_t = K_1 \left(\frac{1-\beta}{1+\alpha-\beta} e^{-(k_2+k_3)t} + \frac{\alpha}{1+\alpha-\beta} e^{-k_{el}t}\right) \otimes C_p \quad (2)$$

where, $\alpha \equiv k_3/k_2, \beta \equiv k_{el}/k_2$.

The time-course of concentration of total radioactivity is characterized by two coefficients and two time constants ($1/k_2 + k_3$ and $1/k_{el}$). Both the coefficients can be described by an α- and a β-value. On the other hand, the C_t may also be characterized by the ratio of the two time constants, i.e. γ-value ($\equiv k_{el}/(k_2 + k_3)$). Thus, we considered that the two kinetic parameters, the β- and the γ-value, of a given tracer would affect the precision of k_3 estimation. However, we mainly focused on the β-value, because the optimal β condition was found to be more important than the γ condition in terms of tracer sensitivity. As such, we felt that the γ-value should be dealt with separately (see Supplementary data for details).

Simulation study

Generation of TACs for simulations

We performed a Monte Carlo simulation study. Noise-free-TACs for a target were generated using Eq. (1) with the given K_1, k_2, k_3 and k_{el} parameter values and a typical [^{11}C]MP4A plasma input curve from a healthy human subject (Iyo et al., 1997; Namba et al., 1999). The dynamic sequence was set as follows: 3×20 s, 3×40 s, 1×60 s, 2×180 s, 5×360 s, 2×600 s. Based on a previous report (Logan et al., 2001), additive noise for simulated TAC was generated by the following equation:

$$\sigma_i = \varepsilon \sqrt{\frac{C_i}{\Delta t_i \cdot e^{-\lambda t_i}}} \times (xx) \quad (3)$$

where ε indicates the scale factor that determines noise level, t_i indicates the mid-scan time, Δt_i indicates the scan duration time, C_i indicates noise-free simulated radioactivity concentration at frame number i, λ indicates the ^{11}C decay constant, and (xx) are pseudo random numbers from a Gaussian distribution N(0,1). To generate the TACs for the simulations (simulated TACs), the random noise derived from Eq. (3) was added to each time point of the noise-free TAC. The scale factor was adjusted as the coefficient of variation (CV(%) = SD/mean × 100) of the k_3 parameter, being approximately 10% when the k_{el}-value is 0.00001 min^{-1}, based on data from a previous PET study using [^{11}C]MP4A in human cortex (Nagatsuka et al., 2001). A weighted non-linear least square (NLS) analysis using the Marquardt algorithm (Levenberg, 1944; Marquardt, 1963) was performed to estimate k_3 from a simulated TAC.

Effect of tracer α-value on precision of k_3 estimation

The simulation study was performed to examine the effect of the α-value of a given tracer on the precision of a k_3 estimate. Simulated TACs were generated using the values of rate constants, set as follows: $K_1 = 0.54$ mL g^{-1} min^{-1}, $k_2 = 0.13$ min^{-1}, based on the previous human PET study using MP4A (Iyo et al., 1997). The k_3 parameter was altered so that the α-value varied from 0.001 to 10 under each β condition altered in five levels; 0, 0.00008, 0.08, 0.4 and 0.8 min^{-1} (corresponding to k_{el} conditions; 0, 0.00001, 0.01, 0.05 and 0.1 min^{-1}). The NLS analysis was performed to estimate four rate constants (K_1, k_2, k_3 and k_{el}) simultaneously from a simulated TAC. These processes were repeated to obtain over 300 parameter sets under every k_{el} condition, and the CV and the bias of the estimated parameters were calculated. In addition, we performed the same simulation for an irreversible tracer with the kinetics described by the two-tissue compartment model with three parameters (K_1, k_2 and k_3).

Precision and bias of k_3 estimate from simultaneous estimation of four rate constants

Simulated TACs were generated using the values of rate constants; $K_1 = 0.54$ mL g^{-1}min^{-1}, $k_2 = 0.13$ min^{-1}, $k_3 = 0.079$ min^{-1} based on a previous human PET study for MP4A (Iyo et al., 1997). The k_{el}-value was altered so that the β-value was changed from about 0.00008 to 0.8 as described above. The NLS analysis was performed to estimate simultaneously four rate constants (K_1, k_2, k_3 and k_{el}) from a simulated

TAC. The CV of k_3 estimation was calculated in the same manner as described above.

Monkey PET study

[^{11}C]MP4A, [^{18}F]FEP-4MA and the alcoholic metabolite of [^{18}F]FEP-4MA were prepared as described previously (Namba et al., 1999; Kikuchi et al., 2005). Physostigmine was purchased from Sigma-Aldrich Japan K.K. (Tokyo, Japan). All other chemicals were of reagent grade or better, and were available commercially.

A male monkey (*Macaca mulatta*, 20 years old, 7 kg) served as the subject in this experiment, and was maintained and handled in accordance with the guidelines of the National Institute of Radiological Sciences (NIRS). The present study was approved by the Animal Ethics Committee of NIRS, Chiba, Japan.

PET scans were performed using a high-resolution SHR-7700 PET camera (Hamamatsu Photonics, Japan; 31 transaxial slices 3.6 mm (center-to-center) apart, a 33.1-cm field of view, 111.6-mm axial field of view, spatial resolution of 2.6 mm full width at half maximum) designed for laboratory animals. The monkey was fixed on a chair in an unanesthetized condition throughout the PET session, and was immobilized with a fixation device to ensure accuracy of repositioning. After transmission scans for attenuation correction using a ^{68}Ge–^{68}Ga source, a dynamic scan in enhanced 2D mode was performed for 60 min. A dynamic sequence of 3×20 s, 2×30 s, 4×60 s, 2×180 s, and 5×480 s scans was used. One mL of each tracer solution, [^{11}C]MP4A (780 MBq) and [^{18}F]FEP-4MA (330 MBq), was infused via the crural vein for 1 min. Emission data were reconstructed with a 4.0-mm Hanning filter. Concentrations of radioactivity (%ID/mL) in the occipital cortex, cerebellum and striatum were measured, and these corresponded to regions with low, middle and high acetylcholinesterase activity, respectively. In the occipital cortex, six regions of interest (ROIs) were also sampled. To confirm the extent to which penetration of the alcoholic [^{18}F]FEP-4MA metabolite from the blood to the brain occurred, a dose of the metabolite (230 MBq) was administrated to the monkey and the concentration of radioactivity in the whole brain was determined.

Approximately 0.5 mL of arterial blood was drawn from the artery cannula into 1 mL heparinized syringes, and the blood samples were immediately transferred into tubes containing the cholinesterase inhibitor physostigmine (0.1 mg in 10 μL saline). The blood samples were drawn at 15 s, 32 s, 41 s, 56 s, 65 s, 76 s, 100 s, 120 s, 144 s, 170 s, 191 s, 215 s, 245 s, 280 s, 311 s, 340 s, 397 s, 457 s, 523 s, 583 s, 642 s, and 1,245 s after starting [^{11}C]MP4A administration, and 26 s, 37 s, 50 s, 57 s, 69 s, 93 s, 117 s, 135 s, 159 s, 191 s, 209 s, 237 s, 300 s, 367 s, 424 s, 482 s, 541 s, 607 s, 901 s, and 1,207 s after starting [^{18}F]FEP-4MA administration. Then, 50 μL of plasma samples, which was obtained by centrifuging the blood sample at $10{,}000\times g$ for 10 min, was mixed with 0.1 mL of ethanol and centrifuged at $10{,}000\times g$ for 10 min. A portion of the plasma sample was subjected to thin layer chromatography (TLC) with a silica-gel plate (silica gel 60 F254; Merck Ltd., Tokyo, Japan) and a mixture of ethyl acetate:iso-propanol:28% ammonia (15:5:1 volumes for [^{11}C]MP4A, 100:10:1 volumes for [^{18}F]FEP-4MA) as a developing solvent. The fraction of the authentic compounds in the plasma sample was detected quantitatively using radio-TLC analysis (BAS 5000, FUJIFILM Co., Tokyo, Japan). In addition, radioactivity in 150 μL of each intact plasma sample was measured with a gamma counter (Wizard; PerkinElmer Co., Ltd. Kanagawa, Japan).

Each rate constant was estimated by NLS analysis in the same manner as performed for the simulation. The data of authentic tracer in blood plasma were fitted by a multiexponential function as previously reported (Namba et al., 1999). The time delay between PET measurement and arterial plasma measurement was corrected using a method described by Iida et al. (1988). The blood volume in the brain was fixed at 3% (Tsukada et al., 1999). Standard errors (SE) of estimated k_3 parameters, uncertainty of the parameter value because of fitting error, were calculated using the covariance matrix (Carson, 1986).

Results

The effect of tracer α-value on the precision of a k_3 estimate

We investigated how tracer α-value affected k_3 precision under different k_{el} conditions. The results revealed that tracer α-value was one of the critical factors determining k_3 precision (Fig. 2A), and the optimal α-value with the maximal precision of k_3 parameter was around 0.5. The high precision of k_3 estimates was maintained when the tracer α-value was within a range of approximately 0.2 to 1.0 (optimal α range). The tracer β-value strongly affected the precision of the k_3 estimate (Fig. 2A). The tracer α-value also affected TAC sensitivity for k_3 changes (Fig. 2B). In addition, when the two-tissue compartment model with three parameters was used in the analysis (i.e. using an irreversible tracer), the optimal α-value was slightly reduced to a lower value (around 0.2) compared with that using the two-tissue compartment model with four parameters (around 0.5; Fig. 2A). The precision of the k_3 estimate in irreversible tracers was higher than that in incomplete trapping irreversible tracers throughout the whole α range. The difference between the k_3 precision of an irreversible tracer and an incomplete one was decreased with increases in tracer α-value.

Effect of tracer β-value on precision and bias of estimated k_3

The precision of k_3 estimates was highly dependent on the β-value of a given tracer (Fig. 3A). The precision of k_3 was primarily determined by the β-value rather than the k_{el}-value of a given tracer alone (Supplementary Fig. A), and was drastically decreased when the β-value was over 0.1 (Fig. 3A, Supplementary Fig. A). The tracer β-value was also found to be a critical factor in the sensitivity of TAC. The change in TAC shapes with a 30% decreased k_3 became larger as the β-value decreased (Fig. 3B). The change in TAC shapes became obscure as the β-value increased, especially over around 0.1 of the β-value (Fig. 3B). The positive bias of the k_3 estimate was drastically increased when the tracer β-value was over approximately 0.4 (Fig. 3A).

Monkey PET study

Fig. 4 shows TACs for both [^{18}F]FEP-4MA and [^{11}C]MP4A in the cerebellum, striatum and occipital cortex. The proportion of regional uptake of both tracers in the three areas was: striatum>cerebellum>cortex, indicating the relative acetylcholinesterase activity in the different regions. The differences in the TAC values for [^{11}C]MP4A at the later phase in the different regions (Fig. 4B) was larger than those for [^{18}F]FEP-4MA (Fig. 4A). On the other hand, the radioactivity in the monkey brain remained low during the observation period when the alcoholic metabolite of [^{18}F]FEP-4MA was administrated (Fig. 4A).

Fig. 5 shows TACs for each of [^{18}F]FEP-4MA and [^{11}C]MP4A in the arterial plasma and occipital cortex. Both tracers disappeared from the arterial blood within 15 min of the injection (Fig. 5A). In the early phase after intravenous injection, the uptake of [^{18}F]FEP-4MA into brain tissue was higher than that of [^{11}C]MP4A (Fig. 5B). For [^{18}F]FEP-4MA, the K_1 and k_{el}-values were larger than those observed for [^{11}C]MP4A (Table 1). In particular, the k_{el}-value of [^{18}F]FEP-4MA was more than three times as large as the k_{el}-value for [^{11}C]MP4A.

The k_{el}-value for [^{18}F]FEP-4MA (0.012 min^{-1}) was relatively low compared with the k_2-values, resulting in a low β-value (=0.085). The precision of k_3 parameter was high for [^{18}F]FEP-4MA (7.4%) and [^{11}C]MP4A (10%).

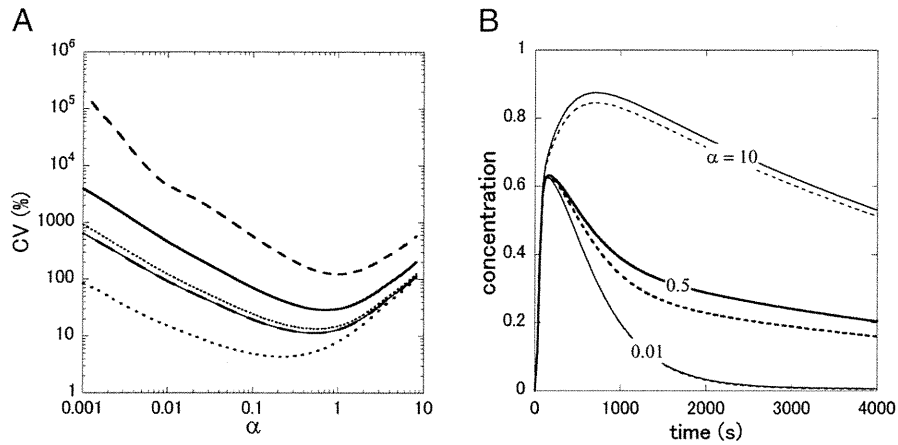

Fig. 2. Dependency of k_3 precision (A) and TAC sensitivity for k_3 change (B) on tracer α-value. (A) The vertical axis represents the coefficient of variation (CV(%)) of k_3 parameter and horizontal represents logarithms of the tracer α-value. In this calculation, K_1 and k_2 are constants ($K_1 = 0.54$, $k_2 = 0.13$). Each plotted line estimated using two-tissue compartment model with four parameters corresponds to the conditions of tracer β-values; 0 (bold broken line), 0.00008 (thin solid line), 0.08 (thin dotted line), 0.4 (bold solid line), 0.8 (bold broken line). The former two graphs are almost same. The bold dotted line corresponds to the curve estimated using two-tissue compartment model with three parameters in the case of $\beta = 0$. (B) Three pairs of TACs for incomplete trapping irreversible tracer with different α-values (0.01, 0.5, 10) are calculated using Eq. (1) with the same input function and rate parameter set (K_1, k_2, k_3, β) = (0.54, 0.13, C, 0.08; solid line) or (0.54, 0.13, 0.7 × C, 0.08; broken line). C indicates the k_3-value corresponding to each α-value.

Discussion

The present study investigated how the incomplete trapping of tracer metabolites in a target tissue affects the sensitivity of detecting the activity of a target enzyme (i.e. the k_3 parameter), using both simulations and a monkey PET study. In addition to the α-value, we used the β-value as kinetic parameter related to the extent of the elimination of tracer metabolites. The α-value refers to the ratio of metabolic rate to the efflux rate of authentic tracer, and determines the sensitivity of an irreversible tracer (Koeppe et al., 1999). In contrast, the β-value is the ratio of elimination rate to efflux rate. Theoretical models predict that the β-value also affects the precision of k_3 estimates: when the tracer β-value changes to 1, estimation of the k_3 parameter becomes impossible. As such, testing this value involved in the k_{el}-value may help to elucidate the effects of the elimination of the tracer metabolite on the precision of k_3 estimates.

In the simulation study, we found that the tracer α-value was still the critical kinetic parameter for determining k_3 precision with incomplete trapping irreversible tracers, and precision became high when the α-value was within the range of approximately 0.2 to 1.0 regardless of the tracer β-value. The optimal range with incomplete trapping irreversible tracers was found to be slightly higher than that of irreversible tracers. In addition, the results of the simulation revealed that the optimal α-value of irreversible tracers was around 0.2, in accord with previous reports that the precision of k_3 estimation is high in irreversible tracers when the α-value is within the range of 0.1–0.3 for [^{11}C]PMP (Koeppe et al., 1999) and 0.14–0.6 for [^{11}C] clorgyline (Logan et al., 2002). When the α-value of a given tracer was far from the optimal α-value, the TAC of the tracer became insensitive to k_3 change. When a tracer α-value is extremely low, the change in TAC shape corresponding to k_3 change becomes small, resulting in a k_3 estimate with low precision. A decrease of k_3 precision is also caused under high α conditions, because the net incorporation of the tracer with a high α-value into a target tissue will be dependent not on metabolic rate (k_3), but on a blood flow (K_1) (i.e. a delivery limitation effect).

We conducted a simulation study to investigate how the tracer β-value (or k_{el}-value) affects k_3 precision. We found that the precision of k_3 estimates was highly dependent on the k_{el}-value. Specifically, precision was largely determined by the β-value of the tracer: when

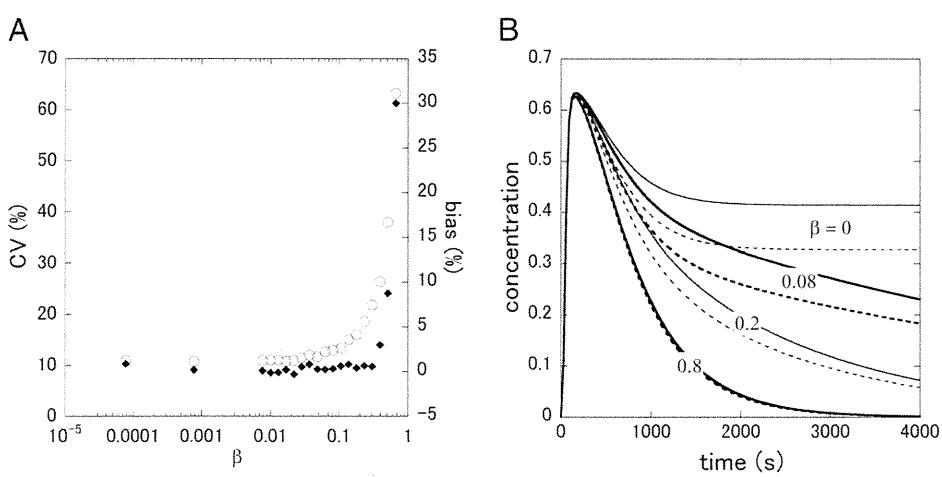

Fig. 3. Dependency of precision and bias of k_3 estimate (A) and dependency of TAC sensitivity for k_3 change (B) on the β-value of a tracer. (A) The vertical axis on the left side represents the CV of the k_3 parameter. The vertical axis on the right side represents the k_3 bias, and the horizontal axis represents logarithms of the β-value of the tracer. Open circles indicate k_3 precision and closed diamonds indicate k_3 bias. (B) Dependency of TAC sensitivity for k_3 change on β-values of a tracer. Four pairs of TACs for incomplete trapping irreversible tracer with different β-values are calculated using Eq. (1) with the same input function and rate parameter set (K_1, k_2, k_3) = (0.54, 0.13, 0.079; solid line) or (0.54, 0.13, 0.7 × 0.079; broken line) and different β-values (0, 0.08, 0.2, and 0.8).