

# Dopamine D<sub>1</sub> Receptors and Nonlinear Probability Weighting in Risky Choice

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Misestimating risk could lead to disadvantaged choices such as initiation of drug use (or gambling) and transition to regular drug use (or gambling). Although the normative theory in decision-making under risks assumes that people typically take the probability-weighted expectation over possible utilities, experimental studies of choices among risks suggest that outcome probabilities are transformed nonlinearly into subjective decision weights by a nonlinear weighting function that overweights low probabilities and underweights high probabilities. Recent studies have revealed the neurocognitive mechanism of decision-making under risk. However, the role of modulatory neurotransmission in this process remains unclear. Using positron emission tomography, we directly investigated whether dopamine D<sub>1</sub> and D<sub>2</sub> receptors in the brain are associated with transformation of probabilities into decision weights in healthy volunteers. The binding of striatal D<sub>1</sub> receptors is negatively correlated with the degree of nonlinearity of weighting function. Individuals with lower striatal D<sub>1</sub> receptor density showed more pronounced overestimation of low probabilities and underestimation of high probabilities. This finding should contribute to a better understanding of the molecular mechanism of risky choice, and extreme or impaired decision-making observed in drug and gambling addiction.

## Introduction

Life is filled with risks. Should I take an umbrella with me this morning? Should I buy car insurance? Which therapy or medicine will improve my health? To answer these questions, and choose, weighting the probability of the possible outcomes is crucial. In particular, misestimating risk could lead to disadvantaged choices such as initiation of drug use (or gambling) and transition to regular drug use (or gambling) (Kreek et al., 2005).

Normative theory in decision-making under risks assumes that people combine probabilities and valuation (utility) of possible outcomes in some way, most typically by taking the probability-weighted expectation over possible utilities. While this expected utility theory (von Neumann and Morgenstern, 1944) is the dominant model, a substantial body of evidence shows

that decision makers systematically depart from it (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). In the prospect theory, objective probabilities,  $p$ , are transformed nonlinearly into decision weights  $w(p)$  by a weighting function. Experimental estimates suggest the weighting function is regressive, asymmetric, and inverse S-shaped, crossing the diagonal from above at an inflection point (about 1/3) where  $p = w(p)$ . 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.

Risky choice is one of the topics explored in a synthesis of economics and neuroscience called neuroeconomics. Neuroeconomics fMRI studies have demonstrated the neural basis for some other features of the prospect theory such as framing effects and loss aversion (De Martino et al., 2006; Tom et al., 2007). Recently, the neural basis for nonlinear weighting function has also been investigated by fMRI. Hsu et al. (2009) reported that the degree of nonlinearity in the neural response to anticipated re-

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ward in the striatum reflected the nonlinearity parameter as estimated behaviorally.

A deeper question is how modulatory neurotransmission is involved in the central process of decision-making (Trepel et al., 2005; Rangel et al., 2008; Fox and Poldrack, 2009). Investigation of the relationship between the dopamine (DA) system and prospect theory seems promising, considering the fact that DA 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 (Zack and Poulos, 2004; Steeves et al., 2009). Trepel et al. (2005) speculated in a thoughtful review that DA transmission in the striatum might be involved in shaping probability weighting. Using positron emission tomography (PET), we tested this speculation directly by investigating how DA D<sub>1</sub> and D<sub>2</sub> receptors in the brain are associated with transformation of probabilities into decision weights. Phasic DA release occurs during reward and reward-predicting stimuli (Grace, 1991; Schultz, 2007). It is suggested that available striatal D<sub>1</sub> receptors are preferentially stimulated by phasically released DA, whereas low-level baseline tonic DA release is enough for stimulating striatal D<sub>2</sub> receptors (Frank et al., 2007; Schultz, 2007). Because estimating reward cue in our task is considered to induce phasic DA release, we hypothesized that the variability of available D<sub>1</sub> receptors might be more associated with individual differences than that of available D<sub>2</sub> receptors.

## Materials and Methods

### Subjects

Thirty-six healthy male volunteers (mean age ± SD, 25.2 ± 4.9 years) were studied. They did not meet the criteria for any psychiatric disorder based on unstructured psychiatric screening interviews. None of the controls were taking alcohol at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. Ten subjects were light to moderate cigarette smokers. All subjects were right-handed according to the Edinburgh Handedness Inventory. The vast majority of subjects were university students or graduate school students (three of the participants had finished university and were employed). All subjects underwent MRI to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all subjects, and the study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

### Procedure

To estimate decision weight, certainty equivalents were determined outside the PET scanner. The behavioral experiment took place 1–2 h before the first PET scans. The procedure was based on the staircase procedure suggested by Tversky and Kahneman (1992), which is the most efficient method for estimating certainty equivalents (Paulus and Frank, 2006; Fox and Poldrack, 2009). 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 (supplemental Fig. 1, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material). Gambles were presented that had an objective probability  $p$  of paying a known outcome  $x$  (and paying zero otherwise). The different combinations of  $p$  and  $x$  are shown in supplemental Table 1, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material. There were 22 gambles, and half of them were 10,000 yen (~\$100) gambles. Because 10,000 yen is the highest-value Japanese paper currency, 11 probabilities were used for 10,000 yen gambles to refine the estimation of weighting function. In each trial, the participants chose between a gamble and a sure payoff. The relative position (left and right) of the two options was randomized to counterbalance for order effects. The subjects were told to make hypothetical rather than actual gambles and were instructed as follows: "Two options for possible mon-

etary gain will be presented to you. Option 1 is a sure payoff and option 2 is a gamble. For example, you will see the guaranteed 6,666 yen on one side of the monitor, and see a gamble in which you have a 50% chance of winning 10,000 yen on the other side. Make a choice between the two options according to your preference by pressing the right or left button. There is no correct answer and no time limit. Once you make a choice, the next options will be presented."

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 iterated to successively narrow the range including the certainty equivalents. The adjustments in the amount of a sure payoff were made in the following manner. The initial range was set between 0 and  $x$  (the gamble outcome). The range was divided into thirds. The one-third and the two-thirds intersecting points of the initial range were used as sure payoff options in trials 1 and 2. If the participant accepted the sure option of the two-thirds and rejected that of the one-third in trials 1 and 2, the middle third portion of the initial range was used as a range for trials 3 and 4. If the participant accepted both sure options of the thirds, the lower third part was then used as a range. If the participant rejected both the sure options of the thirds, the upper third part was then used. The new range was again divided into thirds and the same procedure was iterated until the participant completed trial 8. The mean of the final range was used for a certainty equivalent (supplemental Fig. 2, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material). Once a certainty equivalent was estimated for a given gamble, the next gamble was chosen for estimation, and so on. The order of the gambles was randomized across the participants.

### Behavioral data estimation

According to the prospect theory, the valuation  $V$  of a prospect that pays amount  $x$  with probability  $p$  is expressed as  $v(x, p) = w(p)v(x)$ , where  $v$  is the subjective value of the amount  $x$ , and  $w$  is the decision weight of the objective probability  $p$ . The utility function is usually assumed to be a power function  $v(x) = x^\alpha$  (results are typically similar to other functions). Although several estimations of the nonlinear probability weighting function have been used in previous experiments (Lattimore et al., 1992; Tversky and Kahneman, 1992; Wu and Gonzalez, 1996), 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 function typically fits as well as other functions with one or two parameters (Hsu et al., 2009), and because nonlinearity is fully captured by a single parameter, it is simple to correlate the degree of nonlinearity ( $\alpha$ ) across individuals with biological measures such as receptor density or fMRI signals (Hsu et al., 2009). 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  $1/e$ ). The parameter  $\alpha$  indicates the degree of nonlinearity. A smaller value of  $\alpha$  (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. The weighting function and utility function were estimated by least-squares method.

### PET scanning

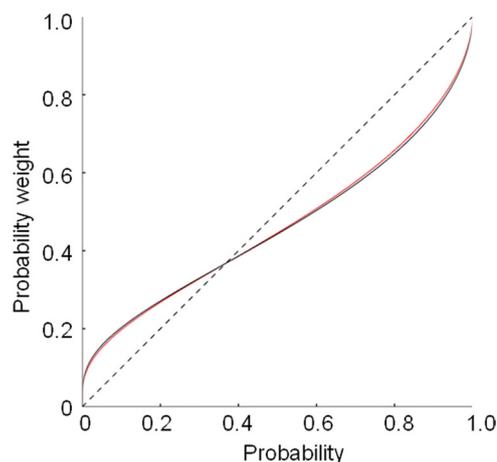
PET studies were performed on ECAT EXACT HR+ (CTI-Siemens). The system provides 63 planes and a 15.5 cm field of view. To minimize head movement, a head fixation device (Fixster) was used. A transmission scan for attenuation correction was performed using a germanium 68–gallium 68 source. Acquisitions were done in three-dimensional mode with the interplane septa retracted. The first group of 18 subjects (mean age ± SD, 24.7 ± 3.8 years) was studied for both D<sub>1</sub> receptors and extrastriatal D<sub>2</sub> receptors. These 18 subjects came to the PET center twice, once each for the studies of [<sup>11</sup>C]SCH23390 (*R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) and [<sup>11</sup>C]FLB457 ((*S*)-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide). For evaluation of D<sub>1</sub> receptors, a bolus of 215.9 ± 9.8 MBq of [<sup>11</sup>C]SCH23390 with specific radioactivities (90.1 ± 38.5 GBq/μmol) was injected intravenously from the antecubital vein with a 20 ml saline flush. The fact that [<sup>11</sup>C]SCH23390 has high affinity for D<sub>1</sub> receptors (Ekelund et al., 2007), and that D<sub>1</sub> receptors are mod-

erately expressed in the extrastriatal regions (approximately one-fifth of striatal D<sub>1</sub> receptor density) (Ito et al., 2008) leads to good reproducibility of both striatal and extrastriatal [<sup>11</sup>C]SCH23390 bindings (Hirvonen et al., 2001). Although [<sup>11</sup>C]SCH23390 is a selective radioligand for D<sub>1</sub> receptors, it has some affinity for 5HT<sub>2A</sub> receptors. However, 5HT<sub>2A</sub> receptor density in the striatum is negligible compared with D<sub>1</sub> receptor density. 5HT<sub>2A</sub> receptor density is never negligible in the extrastriatal regions. Although previous reports in the literature have indicated that [<sup>11</sup>C]SCH23390 affinity for 5HT<sub>2A</sub> receptors relative to D<sub>1</sub> receptors is negligible, a recent *in vivo* study reported that approximately one-fourth of the cortical signal of [<sup>11</sup>C]SCH23390 was due to binding to 5HT<sub>2A</sub> receptors, suggesting that cautious interpretation of the extrastriatal findings regarding this ligand is recommended (Ekelund et al., 2007). For evaluation of extrastriatal D<sub>2</sub> receptors, a bolus of 218.3 ± 13.9 MBq of [<sup>11</sup>C]FLB457 with high specific radioactivities (238.0 ± 100.8 GBq/μmol) was injected in the same way. [<sup>11</sup>C]FLB457 has very high affinity for D<sub>2</sub> receptors. It is a selective radioligand for D<sub>2</sub> receptors and has good reproducibility of extrastriatal D<sub>2</sub> bindings (Sudo et al., 2001). Dynamic scans were performed for 60 min for [<sup>11</sup>C]SCH23390 and 90 min for [<sup>11</sup>C]FLB457 immediately after the injection. Although [<sup>11</sup>C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated since the duration of the [<sup>11</sup>C]FLB457 PET study was not sufficient to obtain equilibrium in the striatum (Olsson et al., 1999; Suhara et al., 1999). For radiation safety reason, striatal D<sub>2</sub> receptors were evaluated in the second group of the other 18 subjects [mean age ± SD, 25.7 ± SD 5.9 years]. A bolus of 218.2 ± 10.1 MBq of [<sup>11</sup>C]raclopride with a specific radioactivity of 451.1 ± 154.6 GBq/μmol was injected similarly. [<sup>11</sup>C]Raclopride is a selective radioligand for D<sub>2</sub> receptors, and has good reproducibility of striatal D<sub>2</sub> bindings (Volkow et al., 1993). Because the density of extrastriatal D<sub>2</sub> receptors is less than one-tenth of striatal D<sub>2</sub> receptors (Ito et al., 2008), [<sup>11</sup>C]raclopride is suitable for the evaluation of striatal D<sub>2</sub> receptors, but not of extrastriatal D<sub>2</sub> receptors, due to its moderate affinity for D<sub>2</sub> receptors. Dynamic scans were performed for 60 min. All emission scans were reconstructed with a Hanning filter cutoff frequency of 0.4 (full width at half maximum, 7.5 mm). MRI was performed on Gyroscan NT (Philips Medical Systems) (1.5 T). T1-weighted images of the brain were obtained for all subjects. Scan parameters were 1-mm-thick, three-dimensional T1 images with a transverse plane (repetition time/echo time, 19/10 ms; flip angle, 30°; scan matrix, 256 × 256 pixels; field of view, 256 × 256 mm; number of excitations, 1).

### Quantification of D<sub>1</sub> and D<sub>2</sub> receptors

Because one subject felt discomfort from the head fixation device during the [<sup>11</sup>C]FLB457 scan, the scan was discontinued and the data of this subject were excluded from the subsequent analysis. Quantitative analysis was performed using the three-parameter simplified reference tissue model (Lammertsma and Hume, 1996; Olsson et al., 1999). This method is well established for [<sup>11</sup>C]SCH23390, [<sup>11</sup>C]FLB457 and [<sup>11</sup>C]raclopride (Lammertsma and Hume, 1996; Olsson et al., 1999) and is widely used (Aalto et al., 2005; Takahashi et al., 2008; McNab et al., 2009; Takahashi et al., 2010), and it allows us to quantify DA receptors without arterial blood sampling, an invasive and time-consuming procedure. The cerebellum was used as reference region because it has been shown to be almost devoid of D<sub>1</sub> and D<sub>2</sub> receptors (Farde et al., 1987; Suhara et al., 1999). The model provides an estimation of the binding potential [BP<sub>ND (nondisplaceable)</sub>] (Innis et al., 2007), which is defined by the following equation:  $BP_{ND} = k_3/k_4 = f_2 B_{max} / \{K_d [1 + \sum_i F_i/K_{di}]\}$ , where  $k_3$  and  $k_4$  describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding,  $f_2$  is the “free fraction” of nonspecifically bound radioligand in brain,  $B_{max}$  is the receptor density,  $K_d$  is the equilibrium dissociation constant for the radioligand, and  $F_i$  and  $K_{di}$  are the free concentration and the dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996). Based on this model, we created parametric images of BP<sub>ND</sub> using the basis function method (Gunn et al., 1997) to conduct voxelwise statistical parametric mapping (SPM) analysis.

In addition to the SPM analysis, we conducted region-of-interest (ROI) analysis. The tissue concentrations of the radioactivities of



**Figure 1.** The fitted probability weighting function with the Prelec model. The red line represents the first group ( $N = 18$  subjects) with D<sub>1</sub> receptors and extrastriatal D<sub>2</sub> receptors investigated. The black line is the second group ( $N = 18$  subjects) whose striatal D<sub>2</sub> receptors were investigated.

[<sup>11</sup>C]SCH23390, [<sup>11</sup>C]FLB457 and [<sup>11</sup>C]raclopride were obtained from anatomically defined ROIs. The individual MRIs were coregistered on [<sup>11</sup>C]SCH23390, [<sup>11</sup>C]FLB457 and [<sup>11</sup>C]raclopride PET images of summed activity for 60, 90 and 60 min, respectively. The ROIs were defined on coregistered MRI with reference to the brain atlas. Given our hypothesis from the previous literature (Hsu et al., 2009), the ROIs were set on the striatum (caudate and putamen). Manual delineation of caudate and putamen ROIs was based on the dorsal caudate and dorsal putamen criteria, respectively, of Mawlawi et al. (2001). The average values of right and left ROIs were used to increase the signal-to-noise ratio for the calculations.

### Statistical analysis

**SPM analysis.** Parametric images of BP<sub>ND</sub> of [<sup>11</sup>C]SCH23390, [<sup>11</sup>C]FLB457 and [<sup>11</sup>C]raclopride were analyzed using the SPM2 software package (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (MathWorks). Parametric images of BP<sub>ND</sub> were normalized into MNI (Montreal Neurological Institute) template space. Normalized BP<sub>ND</sub> images were smoothed with a Gaussian filter to 8 mm full-width half-maximum. Using each of the individual behavioral parameters ( $\alpha$  and  $\sigma$ ) as covariate, regression analyses with the BP<sub>ND</sub> images and the covariates were performed. A statistical threshold of  $p < 0.05$  corrected for multiple comparisons across the whole brain was used, except for a priori hypothesized regions, which were thresholded at  $p < 0.001$  uncorrected ( $r > 0.68$ ) for examination of effect size (only clusters involving 10 or more contiguous voxels are reported). These a priori ROIs included the caudate and putamen.

**ROI analysis.** Pearson's correlation coefficients between BP<sub>ND</sub> of [<sup>11</sup>C]SCH23390 and [<sup>11</sup>C]raclopride in the ROIs and behavioral parameters ( $\alpha$  and  $\sigma$ ) were calculated using SPSS software. Because some subjects were smokers, we further calculated partial correlation coefficients between BP<sub>ND</sub> of [<sup>11</sup>C]SCH23390 and [<sup>11</sup>C]raclopride and behavioral parameters to control for the potential influence of smoking (number of cigarettes per day).

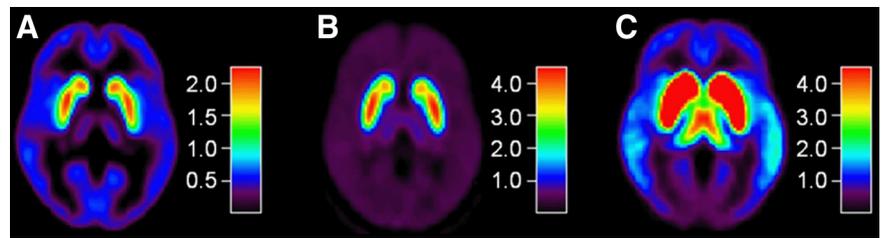
## Results

In the first group, with D<sub>1</sub> receptors and extrastriatal D<sub>2</sub> receptors investigated, the mean (SD)  $\alpha$  of the weighting function and  $\sigma$  of the utility function were 0.58 (0.16) and 0.99 (0.33), respectively. The second group, in which striatal D<sub>2</sub> receptors were investigated, the mean (SD)  $\alpha$  and  $\sigma$  were 0.56 (0.19) and 0.98 (0.18), respectively, indicating that the two groups were comparable. Averaged weighting functions and value functions of the two groups are shown in Figure 1 and supplemental Figure 3 (available at [www.jneurosci.org](http://www.jneurosci.org) as sup-

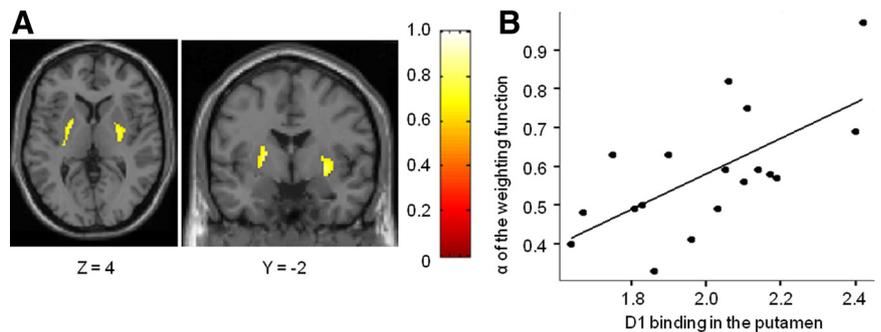
plemental material), respectively. Normalized parametric images of BP<sub>ND</sub> of [<sup>11</sup>C]SCH23390, [<sup>11</sup>C]raclopride and [<sup>11</sup>C]FLB457 are shown in Figure 2A, B, and C, respectively. The mean BP<sub>ND</sub> values of [<sup>11</sup>C]SCH23390 in the caudate and putamen were  $1.86 \pm 0.24$  and  $2.01 \pm 0.22$ , and those of [<sup>11</sup>C]raclopride were  $3.00 \pm 0.32$  and  $3.61 \pm 0.37$ , respectively. Voxel-by-voxel SPM analysis revealed significant positive correlation ( $r > 0.68$ ,  $p < 0.001$ ) between striatal D<sub>1</sub> receptor binding and the nonlinearity parameter  $\alpha$  of weighting function [right striatum, peak (30, -8, -4), 230 voxels; left striatum, peak (-20, -4, 8), 154 voxels] (Fig. 3A). Independent ROI analyses revealed that D<sub>1</sub> receptor binding in the putamen showed a significant correlation with  $\alpha$  (Fig. 3B; Table 1), and D<sub>1</sub> receptor binding in the caudate showed a trend level correlation with  $\alpha$  (Table 1). That is, people with lower striatal D<sub>1</sub> receptor binding tend to be more risk-seeking for low probability gambles and more risk-averse for high probability gambles. SPM analysis showed that extrastriatal D<sub>1</sub> binding was not correlated with  $\alpha$ . SPM and ROI analyses revealed that neither striatal nor extrastriatal D<sub>2</sub> receptor binding was correlated with  $\alpha$ . None of [<sup>11</sup>C]SCH23390, [<sup>11</sup>C]FLB457 and [<sup>11</sup>C]raclopride binding was correlated with the power  $\sigma$  of the value function. Correlation analyses with controlling for the potential influence of smoking revealed identical results, indicating that the influence of smoking was minimal. The results of partial correlation analyses of ROIs between behavioral parameters ( $\alpha$  and  $\sigma$ ) and BP<sub>ND</sub> values of [<sup>11</sup>C]SCH23390 and [<sup>11</sup>C]raclopride in the striatum after controlling for the potential influence of smoking are summarized in supplemental Table 2, available at [www.jneurosci.org](http://www.jneurosci.org) as supplemental material.

## Discussion

We provided the first evidence of a relation between striatal D<sub>1</sub> receptor binding and nonlinear probability weighting during decision-making under risk. Based on circumstantial evidence (Kuhnen and Knutson, 2005; Wittmann et al., 2008) and a speculative review (Trepel et al., 2005), it has been suggested that curvature of the weighting function might be modulated by DA transmission. Utilizing a molecular imaging technique, we directly measured the relation between DA receptors and the nonlinearity of weighting function *in vivo*. Individuals with lower striatal D<sub>1</sub> receptor binding showed more nonlinear probability weighting and more pronounced overestimation of low probabilities and underestimation of high probabilities. Low D<sub>1</sub> receptor binding means that available receptors for phasically released DA are limited. In such case, phasic DA release in response to positive outcomes can stimulate limited D<sub>1</sub> receptors in the striatum. In contrast, low-level baseline tonic DA release is enough for stimulating D<sub>2</sub> receptors (Frank et al., 2007; Schultz, 2007). Therefore, the variability of D<sub>2</sub> receptor binding might have less impact on current behavioral task during which phasic DA release occurs in response to reward cue.



**Figure 2.** Maps of DA D<sub>1</sub> and D<sub>2</sub> BP, averaged across participants (axial slices at the level of Z = 0 of MNI coordinates). **A**, D<sub>1</sub> BP, measured with [<sup>11</sup>C]SCH23390 (N = 18 subjects). **B**, Striatal D<sub>2</sub> BP, measured with [<sup>11</sup>C]raclopride (N = 18 subjects). **C**, Extrastriatal D<sub>2</sub> BP, measured with [<sup>11</sup>C]FLB457 (N = 17 subjects). Although [<sup>11</sup>C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated because the duration of the [<sup>11</sup>C]FLB457 PET study was not sufficient to obtain equilibrium in the striatum. The bar indicates the range of BP.



**Figure 3.** Correlation between nonlinearity of probabilities weighting and D<sub>1</sub> binding in the striatum (N = 18 subjects). **A**, Image showing regions of correlation between nonlinearity parameter of weighting function and D<sub>1</sub> binding in the striatum. The bar shows the range of the correlation coefficient. **B**, Plots and regression line of correlation between  $\alpha$  (nonlinearity parameter) and binding potential of the putamen ( $r = 0.66$ ,  $p = 0.003$ ).

**Table 1. Correlation between behavioral parameters ( $\alpha$  and  $\sigma$ ) and BP<sub>ND</sub> values of [<sup>11</sup>C]SCH23390 (N = 18 subjects) and [<sup>11</sup>C]raclopride (N = 18 subjects) in the striatum**

	$\alpha$	$\sigma$
D <sub>1</sub> receptors		
Caudate	0.011 ( $r = 0.582$ )	0.717 ( $r = 0.092$ )
Putamen	0.003* ( $r = 0.658$ )	0.260 ( $r = 0.280$ )
D <sub>2</sub> receptors		
Caudate	0.305 ( $r = 0.256$ )	0.218 ( $r = 0.305$ )
Putamen	0.242 ( $r = 0.291$ )	0.122 ( $r = 0.378$ )

*p* values (correlation coefficients) are shown. \* $p < 0.01$ .

This molecular imaging approach allows us to broaden our understanding of the neurobiological mechanism underlying nonlinear weighting beyond the current knowledge attained by neuroeconomics fMRI. An fMRI study using a value-titration paradigm has shown that differential anterior cingulate activation during estimation of high probabilities relative to low probabilities was positively correlated with Prelec's nonlinearity parameter  $\alpha$  across subjects (Paulus and Frank, 2006). Another fMRI study with risks of electric shocks found similar nonlinear response in the caudate/subgenual anterior cingulate (Berns et al., 2008). More recently, Hsu et al. (2009), using a simpler exposure-choice paradigm, demonstrated that Prelec's nonlinearity parameter  $\alpha$  was negatively correlated with striatal activity during reward anticipation under risk. 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).

Exploring novelty and risk-seeking behavior are, to some extent, desirable and advantageous for the survival and develop-

ment of many species including human (Kelley et al., 2004). Being too risk-averse would lose opportunities to obtain possibly better outcomes. However, excessive risk-seeking may contribute to reckless choices such as initiation of drug use (or gambling) and transition to regular drug use (or gambling) (Kreek et al., 2005). Pathological gambling and drug addiction frequently co-occur, and it is suggested that the neurobiological mechanisms underlying the two conditions overlap (Tammimga and Nestler, 2006; Steeves et al., 2009). In fact, pharmacological therapy for drug addiction has been shown to also be effective when applied to pathological gambling (Tammimga and Nestler, 2006). Animal studies demonstrated that stimulation of D<sub>1</sub> receptors by a selective agonist increased risky choice and blockade of D<sub>1</sub> receptors decreased risky choice in rats. Although D<sub>2</sub> agonist/antagonist showed similar actions, their effects were not as pronounced as those of D<sub>1</sub> agonist/antagonist (St Onge and Floresco, 2009). A human genetic study reported that variants of the gene for D<sub>1</sub> receptors were linked to risky and novelty-seeking behaviors (Comings et al., 1997), although the genes for other subtypes of DA receptors are also linked to those behaviors. More recently, a PET study suggested that reduced D<sub>1</sub> receptor binding may be associated with an increased risk of relapse in drug addiction (Martinez et al., 2009).

The curvature of the weighting function is traditionally explained by the psychophysics of diminishing sensitivity, the idea that sensitivity to changes in probability decreases as probability moves away from the endpoints of 0 and 1 (Tversky and Kahneman, 1992). However, it has also been suggested that emotional responses to gambles influence weighting as well. 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 D<sub>1</sub> binding might be interpreted as showing more “emotional” decision-making.

We used a simple behavioral task with only positive outcomes to estimate weighting function in this study. Any generalization of our findings needs to be approached with caution. We make more complex decisions in the real world where both positive and negative outcomes are possible, and have to pay attention to relative differences in the magnitude of gains and losses. A computational model has suggested that tonic D<sub>2</sub> receptor stimulation in the striatum inhibits response to avoid negative outcomes (Frank et al., 2007), and other neurotransmitters such as serotonin and noradrenaline are thought to be involved in the complex decision-making process (Trepel et al., 2005; Frank et al., 2007; Cools et al., 2008; Doya, 2008). Using behavioral tasks with negative outcomes, future studies to investigate involvements of other neurotransmissions as well as other areas that are related to punishment or negative emotions such as the orbitofrontal cortex, insula and amygdala (Trepel et al., 2005; Pessiglione et al., 2006; Voon et al., 2010) are recommended. Furthermore, our subjects were relatively homogeneous in terms of economic status (the majority were students). Our findings might not be representative of various samples with different background and socioeconomic status. Notwithstanding this limitation, the present study illustrated that molecular imaging can provide a new research direction for neuroeconomics and decision-making studies by more directly investigating the association between striatal DA transmission and nonlinear probability weighting. This approach may shed light on neurotransmission effects on

emotional and boundedly rational decision-making in our daily life. At the same time, understanding the molecular mechanism of extreme or impaired decision-making can contribute to the assessment and prevention of drug and gambling addiction and the development of novel pharmacological therapies for those addictions.

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