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スポーツ・運動の統合失調症の認知機能・高次脳機能障害に対する効果に関する研究

分担研究者　加藤元一郎　慶應義塾大学医学部精神神経科　准教授

研究要旨

スポーツおよび運動が統合失調症の認知機能に与える影響ないしは効果を検討するためには、まず、その基礎的研究として、統合失調症例における意図的運動の特徴を抽出することが重要である。平成20年度の研究では、統合失調症の随意運動障害と認知機能変化との関係を検討する第一歩として、統合失調症において異常が認められるとされる意志作用感(sense of agency)ないしは自他帰属性に関して、健常例における計算論シミュレーション実験を行い、sense of agencyという概念を用いて、行動学的な実験が可能であることを示した。昨年度は、独自の agency 判断課題を作成し、妄想型統合失調症では over-attribution、残遺型で under-attribution、解体型では confusional pattern が示され、臨床型によって異なった sense of agency の障害パターンが明らかにされた。本年度は、指で物を動かす際に感じる触覚の喪失が意思作用感ないしは agency 判断にどのような影響をもたらすかを、新しい課題を作成し検討した。今回の触覚提示デバイスを用いた仮想空間上での物体移動課題では、物体の動き出しのタイミングに変化を与えない場合には、行為の最中における触感覚の有無は自己帰属率に有意な影響を与えなかったが、一方、物体の動きだしのタイミングに遅れがある場合には、目標に向かった行為中における触感覚の存在の有無は、Sense of Agencyに明らかな影響を与えた。これらの結果は、様々な現われをする統合失調症の自我障害の形成機構を随意運動障害という側面から検討する上で興味深い結果である。

A．研究目的

統合失調症の一級症状でみられるような自我障害は、統合失調症に極めて特異的かつ本質的な症状であると考えられている。おり、認知機能障害研究のターゲットとして重要である。近年、統合失調症の自我障害との関連で注目されてきているのが、「sense of agency（意志作用感・自己主体感)」に関する研究である。sense of agencyとは、自己が行為や思考の作用主体（agent）であるという感覚、すなわち自己の身体運動や外界で生じる事象を自己によって制御できるという主観的体験のことである。すなわち、ある状況の下では行為の主体判断に混乱が生じ、人は自分が起こした行動を自己に帰属できない場合や、これとは反対に、自らが行っていない行為を自分に帰属することが報告され

ている(Sato and Yasuda, 2005)。

過去のsense of agency課題の多くは、随意的行為と外的事象（行為の結果）との因果連関における物理的時間を操作し、それに応じてagencyに関する主観的体験の変化について問う課題であった。具体的には、コンピュータを用いて、被験者の操作（key press, joy stickなど）と画面上の行為の結果に時間バイアス(delay)をプログラムしておき、被験者に自己がagentであると感じるかどうかについて問うものである。統合失調症では、このタイプの課題で自他帰属性に関する異常が存在することが報告されていり、また、我々も平成21年度の報告でこれを指摘した。

これらの現象を説明するモデルとして、モーターコントロール理論に基づいたForward Modelがある（(Miall, 1993, Blakemore, 2003, Haggard, 2005)。このモデルでは、自分が意図する行為の結果の予想と実際に起きた行為の結果を脳内で比較し、その差の大小関係で自己帰属性を判断することになる。そのギャップが十分に小さいものであれば、人はその行為を自己に帰属する。fMRIやPETを用いた脳画像の研究からは、脳内に主体判断のためのForward Modelが存在していることが支持されている

このForward Modelによって説明できる現象として、自己の能動的な行動による自己身体感覚の減少(attenuation)が挙げられる。Blakemoreら（1998）は、自分よりも他人にくすぐられたほうが、その感度が大きくなることを指摘し、また、Baysら(2006)は、自己の片方の指で他方の指に触れた場合、その触感覚は外部からの同じ大きさの力を加えられた場合より弱く感じることを明らかにしている。このように、自己身体に向けられた意図的な行動の際の触覚についての感覚の減少は、efferent copyなどの予期的な（predictive）信号を仮定するForward Modelによって説明できるとされている。しかし、触覚に着目したAgencyに関する研究はなおも少なく、またその多くが行為の結果としての触覚により生じるagency判断に関する研究である。key pressやjoy stickの操作という行為を行い、その結果を判断する際には、2つの感覚が生じる。すなわち、行為の結果としての触覚ないしは感覚と、keyやstick行為を行っている間に操作物体から生じる触覚である。そして、この後者、行為の過程における触覚に変化が生じる際にAgencyがどのように変化するかに関しては研究が行われていない。

本研究では、健常者を被験者とし、触覚提示デバイスを用いて仮想空間上に物体をつくり、物体に触れてこれを動かすタスクを行った。そして、Active touchする際に指に感じる触感覚を消失させた場合および行為の結果として現れる視覚刺激に時間遅れが生じた場合に、被験者が行為の結果をどの程度自己に帰属するかを確かめた。

B．研究方法

対象は、14人の健常男性(平均年齢21.3±0.7才)。被験者は全員右利きだった。実験が始まる前に、実験参加とその結果の公表に対する同意をとった。

本実験では、仮想空間上の物体に触れるためにデバイスとしてPHANToM 1.0 (Sensable., Inc）を用いた。PHANToMはDCモータを用いた力覚ディスプレイであり、3自由度の入力と6自由度の出力をもつ。デ

バイスのアーム部先端を動かすことによって、位置座標の入力が可能である。また、DC モータによって、操作者の指に様々な力覚を生じさせることが可能である。PHANToM の制御には専用の制御用ライブラリである Open Haptics Toolkit(Sensable.,Inc) と Visual Studio C++ 2005 express edition(Microsoft)を、オブジェクトの描写には openGL を用いた。これらによって、描写されたオブジェクトとデバイスの位置が一致したときに DC モータを起動させ、被験者は物体に触れている感覚を得られる。データの記録や PHANToM の制御、画像の表示はすべて一台のコンピュータによって行われた。実験参加者は PHANToM の指サックに右手人差し指を差し入れた状態で、ディスプレイ上に表示される合図と同時に指の屈曲運動を行い(Fig.1)、仮想空間上の物体を動かした。次に、運動している物体を観察して、それを動かした主体が誰であるかを答えた。

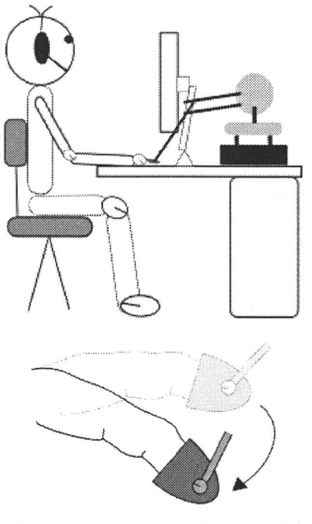

Fig.1 実験環境．上図の指先を拡大したものが下図．

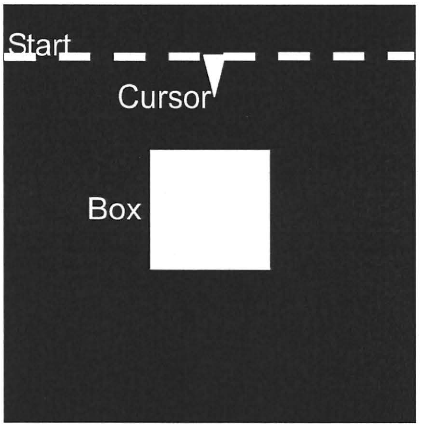

Fig.2 仮想空間上に存在する 3 種類の物体．ここで点線によって表現されている物体が Start であるが，実際の実験系では見ることは出来ない．

仮想空間には以下の三つの物体が存在した(Box, Cursor, Start) (Fig2)。Box は一辺が 3cm の立方体だった。最初は黒色だが、色が赤く変化することによって合図としての役割を果たした。Box の動きは鉛直下向きの等速直線運動に限定されている。動き出しのタイミングに関しては、指が触れた直後に動き出す場合と触れてから 500 ミリ秒後に動き出す二つの場合が存在した。Cursor は仮想空間上における、参加者の指の位置を表示する緑色のオブジェクトだった。実空間上の指サックの動きに対応して動き、合図とともに見えなくなった。Start は Box の上辺から 3cm 上に存在する平面状のオブジェクトだった。Fig.2 では点線で表現されているが、実際には無色透明であり、被験者はディスプレイを通して見ることはできないが、PHANToM を通して触れることが出来た。

被験者は以下の trial を複数回繰り返した(Fig.3)。まず、被験者は PAHNToM を装着した指を Start の下部に触れさせ、その位

置を保持する。その後準備ができたら、逆の手でキーボードのキーを押す。キー押し後、ランダムな時間に(250ms~1500ms)表示される合図がでたら、できるだけ早く指を動かし、Boxに触れるまで指（Cursor）を動かすことが要求された。正常条件(normal task)では、被験者の指がBoxに触れた時に、被験者は必ず触感覚を感じ、それと同時にBoxは下に動き出す。被験者には、Boxは指によってのみ動くということを事前に教示した。Boxが動いたあと、自分がBoxを動かしたか(Sense of Agencyを感じたか)、Boxが自然に動いて落ちたかをキー押しで判断した。はじめに、タスクに慣れることを目的として、100回のnormal taskを施行した。

次に、normal taskを含む4種類の条件をそれぞれ20trialずつ、合計で80trialsの検査が施行された。他の60trial中では，normal taskとは異なる次の1）と2）の2種類の感覚フィードバックが引き起こされた(Fig 4)。

1)Boxに触れた際に感じる触覚の存在の損失

2)Boxに触れた際に物体が運動するタイミングの遅れ

Fig4に示すような4つの条件がランダムに施行された（1条件20trials）。Cursorが物体に触れてからBoxが落ちるまでの間の視覚刺激の時間遅れは､500msに固定した。それぞれの条件において、被験者には、自分がBoxを動かしたかどうかをキー押しでyes/no判断するように要求された。被験者には、自他判断は直感的に行うように注意がなされた。

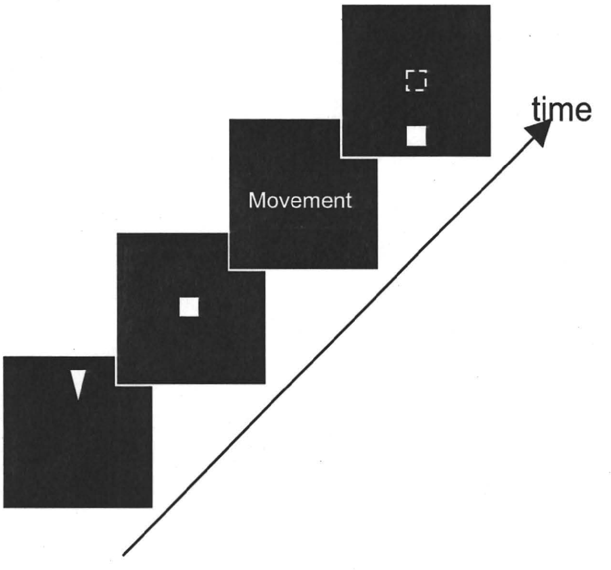

Fig3..実験手続き

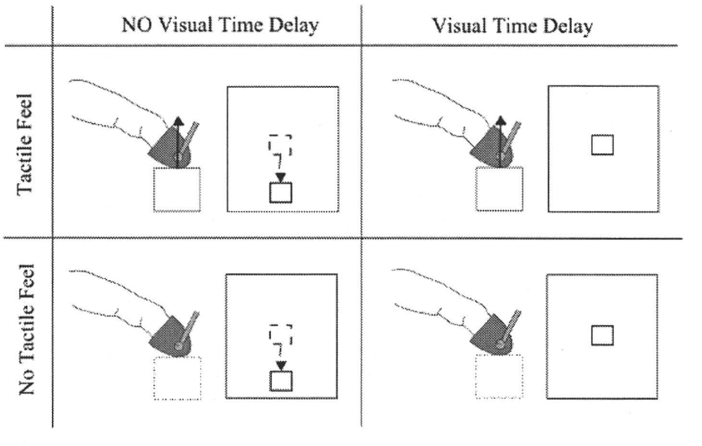

Fig.4 物体と指が触れた瞬間の触覚と視覚フィードバック．実験要因は触感覚有無と時間遅れ有無の二種類．上行の条件ではCursorがBoxに触れたときに指に触感覚を感じるのに対し，下業の条件では触感覚は感じない．左列の条件はCursorがBoxに触れた後，即座に物体が動き出すのに対し，右列の条件では接触後500[ms]後になって動き始める(この時点ではまだ動き始めていない)．ランダムな順番でこれら4種類のtrialを20回ずつ行った.

（倫理面への配慮）

研究参加者に対して、文書で informed consent を得た。その他、倫理面での問題はなかった。

C．研究結果

結果を Fig 5 に示す。横軸が時間遅れの有無，縦軸が Sense of Agency をどれだけ感じたかの割合である。この結果を分散分析によって統計的に評価したところ、時間遅れに関しても触感覚の有無に関しても、統計的に有意な差が見られた($F(1,9)=73.96, p<.005; F(1,13)=29.45, p<.005$)。また、二つの要因の交互作用に関しても有意な差が見られ($F(1,13) = 11.06, p<.01$)。また、単純主効果を計測した結果、Box が動き出すのに 500ms の時間遅れがある場合には触覚の有無に関して有意な差があったにも関わらず($F(1,18) = 37.815, p<.001$)、物体の動きに時間遅れがない場合は、触覚の有無に関して有意な差が見られなかった($F(1,18) = 1.766, p=0.2$)。実際、時間遅れが無い場合には、触覚の有無に関わらず自己帰属率は高い水準を維持したことに対し(M=94.4±7.1%, M=85.8±15.1%)、時間遅れがある場合には触覚の有無によって自己帰属率に大きな違いが観察された(M=60.0±21.1%, M=20.2±17.6%)。

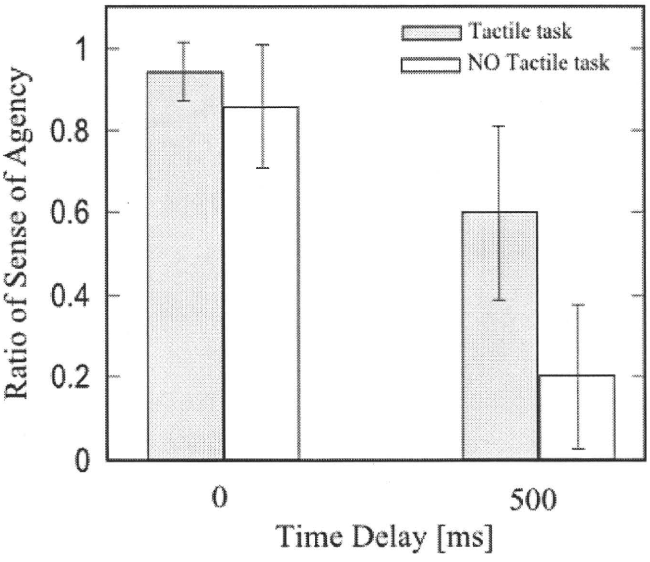

図 5. Fig.5 各トライアルの自己帰属率. 縦軸は 20trials のうち，物体の動きを自己に帰属した割合. エラーバーは標準偏差である. 横軸は指が Box と接触してから Box 動き出すまでの時間. 色のついたバーは物体に触った際に触感覚フィードバックが発生したことを意味し，色のついてないバーは触感覚フィードバックがないことを意味している.

D．考察

本研究では，行為の「結果」となる感覚（視覚）フィードバックだけでなく，行為の「過程」において感覚フィードバック（触覚）に異常を与え、Sense of Agency にどのように変化が起こるかを確かめた。今回の触覚提示デバイスを用いた仮想空間上での物体移動課題では、物体の動き出しのタイミングに変化を与えない場合には、行為の最中における触感覚の有無は自己帰属率に有意な影響を与えなかったが、一方、物体の動きだしのタイミングに遅れがある場合には、目標に向かった行為中における触感覚の存在の有無は、Sense of Agency に

明らかな影響を与えた。

まず、行為の最中における触感覚の有無にかかわらず、視覚的な帰結に時間遅れを与えた場合の自己帰属率の減少については、予想と結果の間にずれが生じると Sense of Agency が減少するという Forward model と矛盾せず、先行研究とも一致している。(Farrer., 2003, Sato and Yasuda., 2005, Wegner., 2003)。すなわち、行為の自他帰属性判断においては、行為の結果のフィードバック情報自体から得られる感覚情報が重要であることを示している。

一方、Box 押しの際の触感覚の欠如に関しては、時間遅れがない場合には Agency に対して有意な差が見られなかったが、時間遅れがある場合には、明らかな自己帰属率の低下が認められた。視覚的な帰結における時間遅れと行為の途中における触覚の欠如が組み合わされると、自己帰属率の大きな減少が認められるのである。この結果は、単純な Forward Model では説明することができない。Sense of Agency を説明するためには、行為の結果とその予測との一致不一致だけではなく、行為を起している間に感じる触覚、すなわち、行為の結果の予期的なレベルにおけるフィードバックの自他帰属性への影響を勘案することが必要と思われた。この現象は、行動の Sense of Agency に関しては、行為の結果の感覚フィードバックの結果のみならず、事前の行為の意図の存在が影響を与えている可能性を示唆している。本実験において被験者に与えられたタスクは「仮想空間上の物体を自分の指の運動によって動かす」というものである。Box の視覚的運動は、行為を起こした後に起こる「結果」のフィードバックと考えられる。一方で，Box に触れる行為は物体を動かすための必要条件であり，そこから得られる触感覚は行為の「過程」から発生すると考えられ、このレベルのフィードバック情報が行為の自己帰属に有意な影響を与えていると考えられる。近年、行動を起こす前の目的の重要性を説明するモデルが提案され始めている(Tsakiris et al 2005)。このモデルでは人間の意図を反映するような Efference Copy や随伴性反射(Corollary Discharge)といった信号が直接的に感覚情報の比較に用いられている可能性を示している。特に、Corollary Discharge は行為を起こす際に、motor neuron よりも高次の脳部位において放出されることが報告されており(Crapse TB and Sommer MA., 2008)、これが人の行為の自己帰属性判断に関わっている可能性も考えられる。

Bays ら (2006) による実空間上のタップの実験機器を用いた指先にかかる力を比較した研究の結果は、本実験の結果を裏付けるものになっている。この研究では、被験者は指に力を加えること によってもう片方の指に力が加えることが出来る機器を用いて，外部から刺激が与えられる場合と自ら行動をした際の指にかかる負荷を比較する検討が行われている。そして、指押し行動をした後に負荷が起こるまでに時間遅れがない場合には、外部刺激と自己行動後刺激の大きさに主観的な差は認められなかった。一方で時間遅れがある場合には、外部刺激よりも自己行動後刺激のほうが負荷を小さく感じることが報告している。Bays ら (2006) は、この現象の原因として、postdictive というよりも行為の事前にある predictive な判断が重要であるとして

いる。

E．結論

人の Sense of Agency を説明するためには、行為の結果とその予測との一致不一致だけではなく、行為を起している間に感じる触覚、すなわち、行為の意図とも関連した結果の予期的なレベルにおけるフィードバックの自他帰属性への影響を考慮することが重要であり、このプロセスを今後モデル化してゆくことが重要と思われた。このことにより、統合失調症における自他帰属性に関する異常がさらに解明されると期待される。

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F．健康危険情報

特に問題なかった。

G．研究発表

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特になし。

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Behavioral/Systems/Cognitive

Dopamine D_1 Receptors and Nonlinear Probability Weighting in Risky Choice

Hidehiko Takahashi,[1,2,3,4] Hiroshi Matsui,[2] Colin Camerer,[5] Harumasa Takano,[2] Fumitoshi Kodaka,[2] Takashi Ideno,[6] Shigetaka Okubo,[6] Kazuhisa Takemura,[6] Ryosuke Arakawa,[2] Yoko Eguchi,[2] Toshiya Murai,[1] Yoshiro Okubo,[7] Motoichiro Kato,[8] Hiroshi Ito,[2] and Tetsuya Suhara[2]

[1]Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan, [2]Molecular Imaging Center, Department of Molecular Neuroimaging, National Institute of Radiological Sciences, Chiba, 263-8555, Japan, [3]Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Saitama, 332-0012, Japan, [4]Brain Science Institute, Tamagawa University, Tokyo, 194-8610, Japan, [5]Division of Humanities and Social Sciences, California Institute of Technology, Pasadena, California 91125, [6]Department of Psychology, Waseda University, Tokyo, 162-8644, Japan, [7]Department of Neuropsychiatry, Nippon Medical School, Tokyo 113-8603, Japan, and [8]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo 160-8582, Japan

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_1 and D_2 receptors in the brain are associated with transformation of probabilities into decision weights in healthy volunteers. The binding of striatal D_1 receptors is negatively correlated with the degree of nonlinearity of weighting function. Individuals with lower striatal D_1 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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Correspondence should be addressed to Dr. Hidehiko 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.

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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_1 and D_2 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_1 receptors are preferentially stimulated by phasically released DA, whereas low-level baseline tonic DA release is enough for stimulating striatal D_2 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_1 receptors might be more associated with individual differences than that of available D_2 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 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 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 monetary 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 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 $v(x) = x^{\sigma}$ (results are typically similar to other functions). Although several estimations of the nonlinear probability weighing 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 (α) 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 α indicates the degree of nonlinearity. 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. 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_1 receptors and extrastriatal D_2 receptors. These 18 subjects came to the PET center twice, once each for the studies of [^{11}C]SCH23390 (R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine) and [^{11}C]FLB457 ((S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide). For evaluation of D_1 receptors, a bolus of 215.9 ± 9.8 MBq of [^{11}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 [^{11}C]SCH23390 has high affinity for D_1 receptors (Ekelund et al., 2007), and that D_1 receptors are moderately expressed in the extrastriatal regions (approximately one-fifth of striatal D_1 receptor density) (Ito et al., 2008) leads to good reproducibility of both striatal and extrastriatal [^{11}C]SCH23390 bindings (Hirvonen et al., 2001). Although [^{11}C]SCH23390 is a selective radioligand for D_1 receptors, it has some affinity for $5HT_{2A}$ receptors. However, $5HT_{2A}$ receptor density in the striatum is negligible compared with D_1 receptor density. $5HT_{2A}$ receptor density is never negligible in the extrastriatal regions. Although previous reports in the literature have indicated that [^{11}C]SCH23390 affinity for $5HT_{2A}$ receptors relative to D_1 receptors is negligible, a recent *in vivo* study reported that approximately one-fourth of the cortical signal of [^{11}C]SCH23390 was due to binding to $5HT_{2A}$ receptors, suggesting that cautious interpretation of the extrastriatal findings regarding this ligand is recommended (Ekelund et al., 2007). For evaluation of extrastriatal D_2 receptors, a bolus of 218.3 ± 13.9 MBq of [^{11}C]FLB457 with high specific radioactivities (238.0 ± 100.8 GBq/μmol) was injected in the same way. [^{11}C]FLB457 has very high affinity for D_2 receptors. It is a selective radioligand for D_2 receptors and has good reproducibility of extrastriatal D_2 bindings (Sudo et al., 2001). Dynamic scans were performed for 60 min for [^{11}C]SCH23390 and 90 min for [^{11}C]FLB457 immediately after the injection. Although [^{11}C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated since the duration of the [^{11}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_2 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 ± 10.1MBq of [^{11}C]raclopride with a specific radioactivity of 451.1 ± 154.6 GBq/μmol was injected similarly. [^{11}C]Raclopride is a selective radioligand for D_2 receptors, and has good reproducibility of striatal D_2 bindings (Volkow et al., 1993). Because the density of extrastriatal D_2 receptors is less than one-tenth of striatal D_2 receptors (Ito et al., 2008), [^{11}C]raclopride is suitable for the evaluation of striatal D_2 receptors, but not of extrastriatal D_2 receptors, due to its moderate affinity for D_2 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_1 and D_2 receptors

Because one subject felt discomfort from the head fixation device during the [^{11}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 [^{11}C]SCH23390, [^{11}C]FLB457 and [^{11}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_1 and D2 receptors (Farde et al., 1987; Suhara et al., 1999). The model provides an estimation of the binding potential [$BP_{ND\ (nondisplaceable)}$] (Innis et al., 2007), which is defined by the following equation: $BP_{ND} = k_3/k_4 = f_2\ B_{max}/\{K_d\ [1 + \Sigma_i\ F_i/K_{di}]\}$, 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_{ND} 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 [^{11}C]SCH23390, [^{11}C]FLB457 and [^{11}C]raclopride were obtained from anatomically defined ROIs. The individual MRIs were coregistered on [^{11}C]SCH23390, [^{11}C]FLB457 and [^{11}C]raclopride PET images of summated 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.

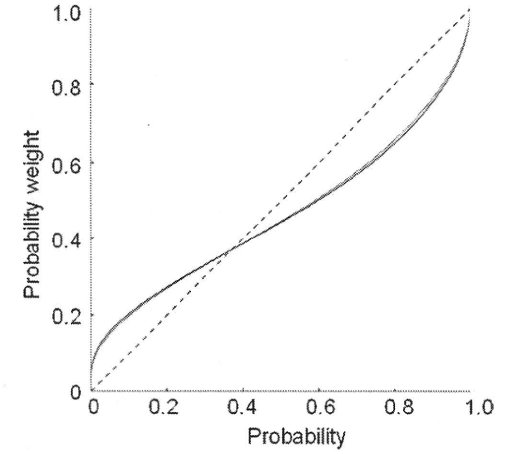

Figure 1. The fitted probability weighting function with the Prelec model. The red line represents the first group ($N = 18$ subjects) with D_1 receptors and extrastriatal D_2 receptors investigated. The black line is the second group ($N = 18$ subjects) whose striatal D_2 receptors were investigated.

Statistical analysis

SPM analysis. Parametric images of BP_{ND} of [^{11}C]SCH23390, [^{11}C]FLB457 and [^{11}C]raclopride were analyzed using the SPM2 software package (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (MathWorks). Parametric images of BP_{ND} were normalized into MNI (Montreal Neurological Institute) template space. Normalized BP_{ND} images were smoothed with a Gaussian filter to 8 mm full-width half-maximum. Using each of the individual behavioral parameters (α and σ) as covariate, regression analyses with the BP_{ND} 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_{ND} of [^{11}C]SCH23390 and [^{11}C]raclopride in the ROIs and behavioral parameters (α and σ) were calculated using SPSS software. Because some subjects were smokers, we further calculated partial correlation coefficients between BP_{ND} of [^{11}C]SCH23390 and [^{11}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_1 receptors and extrastriatal D_2 receptors investigated, the mean (SD) α of the weighting function and σ of the utility function were 0.58 (0.16) and 0.99 (0.33), respectively. The second group, in which striatal D_2 receptors were investigated, the mean (SD) α and σ 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 as supplemental material), respectively. Normalized parametric images of BP_{ND} of [^{11}C]SCH23390, [^{11}C]raclopride and [^{11}C]FLB457 are shown in Figure 2*A*, *B*, and *C*, respectively. The mean BP_{ND} values of [^{11}C]SCH23390 in the caudate and putamen were 1.86 ± 0.24 and 2.01 ± 0.22, and those of [^{11}C]raclopride were 3.00 ± 0.32 and 3.61 ± 0.37, respectively. Voxel-by-voxel SPM analysis revealed significant positive correlation ($r > 0.68$, $p < 0.001$) between striatal D_1 receptor binding and the nonlinearity parameter α of weighting function [right striatum, peak (30, −8, −4), 230 voxels; left striatum, peak (−20, −4, 8), 154 voxels] (Fig. 3*A*). Independent ROI analyses revealed that D_1 receptor binding in the putamen showed a significant correlation with α (Fig. 3*B*; Table 1), and D_1 receptor binding in the caudate showed a trend level correlation with α (Table 1). That is, people with lower striatal D_1 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_1 binding was not correlated with α. SPM and ROI analyses revealed that neither striatal nor extrastriatal D_2 receptor binding was correlated with α. None of [^{11}C]SCH23390, [^{11}C]FLB457 and [^{11}C]raclopride binding was correlated with the power σ 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 (α and σ) and BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]raclopride in the striatum after controlling for the potential influence of smoking are summarized in supplemental Table 2, available at www.jneurosci.org as supplemental material.

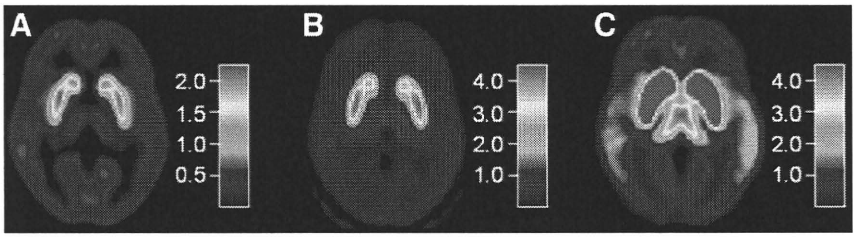

Figure 2. Maps of DA D_1 and D_2 BP, averaged across participants (axial slices at the level of $Z = 0$ of MNI coordinates). ***A***, D_1 BP, measured with [^{11}C]SCH23390 ($N = 18$ subjects). ***B***, Striatal D_2 BP, measured with [^{11}C]raclopride ($N = 18$ subjects). ***C***, Extrastriatal D_2 BP, measured with [^{11}C]FLB457 ($N = 17$ subjects). Although [^{11}C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated because the duration of the [^{11}C]FLB457 PET study was not sufficient to obtain equilibrium in the striatum. The bar indicates the range of BP.

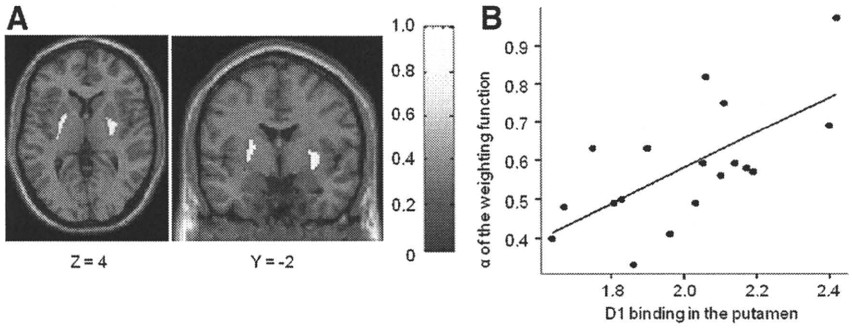

Figure 3. Correlation between nonlinearity of probabilities weighting and D_1 binding in the striatum ($N = 18$ subjects). ***A***, Image showing regions of correlation between nonlinearity parameter of weighting function and D_1 binding in the striatum. The bar shows the range of the correlation coefficient. ***B***, Plots and regression line of correlation between α (nonlinearity parameter) and binding potential of the putamen ($r = 0.66$, $p = 0.003$).

Table 1. Correlation between behavioral parameters (α and σ) and BP_{ND} values of [^{11}C]SCH23390 ($N = 18$ subjects) and [^{11}C]raclopride ($N = 18$ subjects) in the striatum

	α	σ
D_1 receptors		
Caudate	0.011 ($r = 0.582$)	0.717 ($r = 0.092$)
Putamen	0.003* ($r = 0.658$)	0.260 ($r = 0.280$)
D_2 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. *$p < 0.01$.

Discussion

We provided the first evidence of a relation between striatal D_1 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_1 receptor binding showed more nonlinear probability weighting and more pronounced overestimation of low probabilities and underestimation of high probabilities. Low D_1 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_1 receptors in the striatum. In contrast, low-level baseline tonic DA release is enough for stimulating D_2 receptors (Frank et al., 2007; Schultz, 2007). Therefore, the variability of D_2 receptor binding might have less impact on current behavioral task during which phasic DA release occurs in response to reward cue.

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 α 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 α 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 development 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 (Tamminga 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 (Tamminga and Nestler, 2006). Animal studies demonstrated that stimulation of D_1 receptors by a selective agonist increased risky choice and blockade of D_1 receptors decreased risky choice in rats. Although D_2 agonist/antagonist showed similar actions, their effects were not as pronounced as those of D_1 agonist/antagonist (St Onge and Floresco, 2009). A human genetic study reported that variants of the gene for D_1 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_1 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_1 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_2 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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