

Table 1 | Areas exhibiting a stronger response in sympathy scenarios.

Region	Side	MNI coordinates			Z	k	SVC
Posterior cingulate cortex	R	2	-50	28	4.05	2946	0.001
Precuneus	L	-2	-68	42	3.85		
Precuneus	R	0	-18	28	3.73		
Middle frontal gyrus	R	36	16	60	4.11	1501	
Superior frontal gyrus	R	20	32	58	4.08		
Superior frontal gyrus	L	-18	24	64	4.06		
Temporo-parietal junction (middle temporal gyrus)	L	-50	-72	20	4.15	535	0.001
Temporo-parietal junction (angular gyrus)	L	-46	-64	34	3.58		
Inferior frontal gyrus (p. orbitalis)	L	-40	34	-14	4.37	296	
Inferior frontal gyrus (p. triangularis)	L	-50	36	18	3.62		
Inferior frontal gyrus (p. triangularis)	L	-42	34	0	3.54		
Dorsomedial prefrontal cortex (superior medial gyrus)	L	-4	44	22	3.50	217	0.008
Dorsomedial prefrontal cortex (superior medial gyrus)	L	-4	54	28	3.49		
Superior frontal gyrus	L	-12	52	34	3.33		
Caudate nucleus	R	12	18	8	3.82	179	
Hippocampus	R	26	-32	-8	3.47	151	
Parahippocampal gyrus	R	28	-24	-22	3.43		
Caudate nucleus	L	-8	18	2	3.53	101	
Caudate nucleus	L	-12	14	10	3.37		
Middle temporal gyrus	L	-52	4	-32	3.72	81	
Lingual gyrus	R	16	-44	-8	3.50	59	
Parahippocampal gyrus	R	26	10	-30	3.68	48	
Dorsomedial prefrontal cortex (superior medial gyrus)	R	10	44	50	3.37	23	0.011
Superior frontal gyrus	R	16	16	46	44		
Inferior frontal gyrus (p. orbitalis)	L	-26	26	-26	3.56	22	
Temporal pole	L	-36	22	-32	3.19		
Medial temporal pole	R	44	16	-38	3.37	13	
Inferior frontal gyrus (p. orbitalis)	R	38	28	-12	3.22	13	
Temporal pole	L	-34	6	-20	3.17	12	

Abbreviation: SVC, small volume correction.

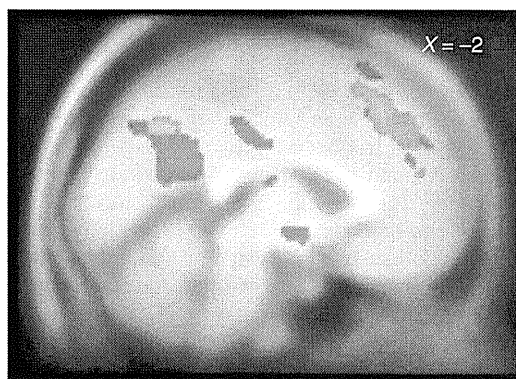
A priori regions of interest are in bold ($P < 0.001$, $k > 10$).

Figure 2 | Brain regions activated during trial-by-trial sympathy and punishment reduction. Regions in which activity correlated with parametric regressors of increasing sympathy (green) and reduced punishment (red). Common areas were found in precuneus (yellow). The image is shown at $P < 0.001$ (uncorrected; $n = 22$, one-sample t -tests).

areas generally associated with moral and cognitive conflicts instead (DMPPFC, precuneus and ACC).

The individual difference analysis showed that activity in the right mid-insula was related to the individual differences on the inclination to mitigate (mapping sympathy to sentences). Middle/posterior insula has been suggested to encode economic inequity³¹, norm violation³², somatosensory representation³³, monitoring internal states³⁴ and heart rate during a compassionate state³⁵. These types of interoceptive processing in middle insula suggest that it is sensitive to emotions linked to sociality. Our study provides unusual evidence of this processing associated with a unique high-impact social judgment that affects others.

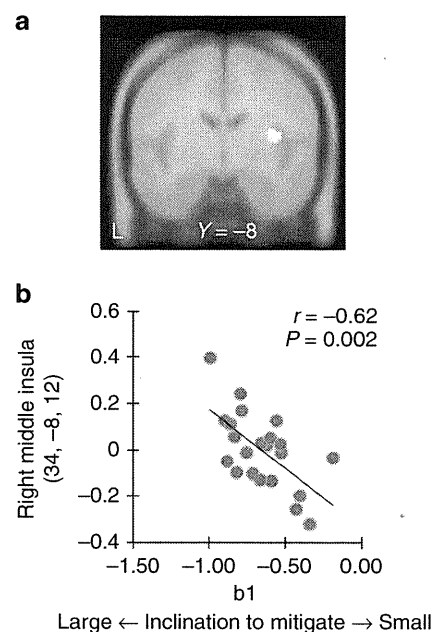


Figure 3 | Individual differences in inclination towards mitigation. Activation in right middle insula in the contrast sympathy minus no-sympathy trials (a, MNI 34/-8/12; $n = 22$, one-sample t -test, $P = 0.023$, small-volume-corrected) correlated with participant-wise coefficient of mitigation (b, $n = 22$, Pearson $r = -0.62$, $P = 0.002$).

The identified brain activity provides new insight into the capacity of the average brain to translate sympathetic feelings into appropriate legal action. A plausible neuro-legal standard is that the influence

of sympathetic reaction on difficult sentencing should recruit brain areas that process sympathy judgments in general, as well as areas that encode difficult decision conflict. Activity in these 'sympathy' regions is evident in our study when judging sympathy alone, and in choosing sentence mitigation. However, not every brain maps sympathy to prison sentences in the same numerical way (as reflected in differential mid-insula activity). Differences in these brain circuits between individuals, suggest that differential juror responses might need to be considered unequally. There is also mixed evidence about the normative basis of legal judgment, including a recent finding that judges' decisions are affected by timing of meals³⁶.

The current finding would also contribute to the attribution literature on situational correction, as there has not been any fMRI work on this. People often attribute behaviour to the corresponding personal disposition, which is, yet, corrected based on situational inducements too³⁷. This is an apt psychological function behind mitigating circumstances that is to make someone less culpable, and the revealed brain activity might be associated with this type of situational correction.

Finally, we note that many legal principles treat emotional responses as likely to be prejudicial and prone to inflammatory manipulation (that is, an ideal juror would suppress them and legal rules limit their influence). Weighing mitigating circumstances during sentencing (*after* a verdict) represents an unusual case in which emotional sympathy judgment is actually required. Japanese criminal law, for example, requires that the decision among these sentences be based on mitigating circumstances³⁸.

Ironically, the fact that sympathy is clearly evident in brain activity, and influences sentence mitigation (as it should), raises interest in the opposite question: can people also suspend emotions when the law instructs them to? More generally, a deeper understanding of the brain could help figure out how highly evolved brain structures, which were sculpted to maintain order in small-scale ancestral societies, can be put to work under modern legal rules in much more challenging cases to create modern justice.

Methods

Participants. A total of 26 right-handed healthy subjects (12 males; mean age = 21.5 ± 1.8 (s.d.) years) participated in the study. All subjects had normal or corrected-to-normal vision, no history of neurological or psychiatric disorder and were not taking medications that interfere with the performance of fMRI. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences (Chiba, Japan). Data from four participants were discarded owing to excessive movement (three subjects) and sleep (one subject). The data from 22 subjects (11 males; mean age = 21.5 ± 1.9 (s.d.) years) were included and analysed.

Stimuli and the task. A total of 32 faces of defendants and criminal acts were prepared in the study. Faces were drawn from a set of Asian face stimuli developed by CAS-PEAL face database³⁹. Pilot participants ($n = 30$) rated attractiveness for each faces using an 11-point scale of -5 (not attractive at all) to +5 (very attractive). The average attractiveness for 32 faces was 0.15 ± 0.70.

All criminal acts were the pure murder cases, which were modified from real stories taken from a precedent search engine provided by Supreme Court of Japan (www.courts.go.jp) and from news articles on the web. We prepared 32 scenarios and consulted a judicial expert for advice on how externally valid the scenarios were. Each scenario composed of the fact (when, where and to whom) and the circumstance (why the defendant committed the murder). Half of the scenarios would induce sympathy for the defendants who suffer from domestic violence, death to disease or poverty (sympathy scenarios), and the other half that would not (no-sympathy scenarios). Responsibility, intentionality and severity of crime were matched between scenarios (see Supplementary Methods for all scenarios used in the study).

Subjects were instructed to judge crimes as if they were jurors (lay judges). Before entering the scanner, subjects read each criminal case and were asked to indicate if they have known them through media. The aim of this session was to ensure and ease comprehension in the scanner that constrain duration of presenting each scenario. During the fMRI task, subjects read each scenario and rated how much they would like to reduce or increment the sentence (all 20 years) given for the defendant using a VAS (with scores ranging from 0 = reduce as much as possible to 100 = increment as much as possible, and 50 = given sentence of 20 years; Fig. 1a). We chose a sentence of 20 years as a reference point, based on a sentencing

guideline in Japan that gives 20 years in prison to a person who commits murder. Defendants' faces were presented together with the scenarios in order to make the experimental setting more realistic and to help participants to dedicate to the study. They completed two sessions, and each session contained 8 sympathy and 8 no-sympathy scenarios, 16 trials in total. The presentation of each scenario within a session was pseudorandomized. The order of sessions and the combination of faces and circumstance types were counterbalanced between subjects.

After the scan, subjects were shown the same scenarios again to rate how much they felt sympathy for the defendants using a VAS (with scores ranging from 0 = having no sympathy to 100 = having sympathy very much). They were also asked to fill out Interpersonal Reactivity Index (IRI), a self-report measure of dispositional empathy.

fMRI data acquisition. The functional imaging was conducted using a GE 3.0 Tesla Excite system to acquire gradient echo T2*-weighted echoplanar images with blood oxygenation level-dependent contrast. Each volume comprised 35 transaxial contiguous slices with a slice thickness of 3.8 mm to cover almost the whole brain (flip angle, 75; echo time, 25 ms; repetition time, 2000 ms; matrix, 64°64; and field of view, 24×24 cm²).

fMRI data preprocessing. Image analysis was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK), except for the overlay image shown in Fig. 2 that was created using the MRICron software (<http://www.sph.sc.edu/comd/rorden/mricron/>). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalised to the standard space defined by the Montreal Neurological Institute (MNI) template. After normalisation, images were spatially smoothed using a Gaussian kernel with a full-width-at-half-maximum of 8 mm. Intensity normalisation and high-pass temporal filtering (using a filter width of 128 s) were also applied to the data.

Generalized linear model. For the primary whole-brain analyses, two modelling approaches were used. In the first approach, trials from each of the sympathy and no-sympathy circumstances were modelled as separate conditions. This allowed separate estimation of the evoked response for each of the conditions at each voxel. The model also included regressors for face, criminal evidence, punishment, and fixation, as well as six head-motion parameters as regressors of no interest. We first calculated a first-level single-subject contrast for reading sympathy minus no-sympathy circumstances. Then, we calculated a second-level group contrasts using a one-sample t -test. In the second approach, all trials from reading circumstances modelled using a single condition (that is, overall task-related activation), and two additional orthogonal parametric regressors were included representing (a) the amount of reducing punishment and (b) the level of sympathy rating. We first calculated first-level single-subject contrasts for reading circumstances modulated by reducing punishment and for reading circumstances modulated by sympathy rating. Then, we calculated second-level group contrasts using one-sample t tests on the single-subject contrasts to identify brain regions whose activation correlated with the amount of reducing punishment and the sympathy rating.

A statistical threshold of $P < 0.05$ corrected for multiple spatial comparisons across the whole brain at cluster level was used, except for a priori hypothesized regions that were voxel thresholded at $P < 0.001$ uncorrected (only clusters involving $k > 10$ or more contiguous voxels were reported⁴⁰). Small volume correction (a 10-mm radius sphere) was used on a priori regions of interest: DMPFC/ACC, precuneus/posterior cingulate cortex, TPJ and the insula.

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Author contributions

M.Y. and H.T. designed the experiment. M.Y. and F.S. prepared and conducted the experiment. M.Y. analysed the data and wrote the paper. C.F.C. edited the manuscript. H.T. coordinated subject recruitment. All authors discussed the results.

Additional information

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Functional Deficits in the Extrastriate Body Area During Observation of Sports-Related Actions in Schizophrenia

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Exercise and sports are increasingly being implemented in the management of schizophrenia. The process of action perception is as important as that of motor execution for learning and acquiring new skills. Recent studies have suggested that body-selective extrastriate body area (EBA) in the posterior temporal-occipital cortex is involved not only in static visual perception of body parts but also in the planning, imagination, and execution of actions. However, functional abnormality of the EBA in schizophrenia has yet to be investigated. Using functional magnetic resonance imaging (fMRI) with a task designed to activate the EBA by sports-related actions, we aimed to elucidate functional abnormality of the EBA during observation of sports-related actions in patients with schizophrenia. Twelve schizophrenia patients and 12 age-sex-matched control participants participated in the study. Using sports-related motions as visual stimuli, we examined brain activations during observation of context-congruent actions relative to context-incongruent actions by fMRI. Compared with controls, the patients with schizophrenia demonstrated diminished activation in the EBA during observation of sports-related context-congruent actions. Furthermore, the EBA activation in patients was negatively correlated with the severity of negative and general psychopathology

symptoms measured by the Positive and Negative Syndrome Scale. Dysfunction of the EBA might reflect a difficulty in representing dynamic aspects of human actions and possibly lead to impairments of simulation, learning, and execution of actions in schizophrenia.

Key words: body/extrastriate body area/schizophrenia/sports/exercise/fMRI

Introduction

With the introduction of atypical antipsychotics, awareness of these comorbid metabolic disturbances in schizophrenia has become considerably increased among many health care professionals and patients.¹ For the management of comorbid metabolic disturbances, exercise is one of the most acknowledged interventions.² At the same time, exercise and sports have been recognized as having a positive impact on the treatment and rehabilitation of schizophrenia.³ However, individuals living with schizophrenia are less physically active than the general population.^{4,5} Moreover, they generally show psychomotor poverty and clumsiness⁶ and have an impairment of motor skill learning,^{7,8} which have been suggested to be linked to a dysfunctional motor execution system including the striatum-frontal-cerebellum.^{9,10}

It is widely documented in psychological and neurocognitive studies that the systems that mediate action perception, imitation, planning, and execution overlap and interact with each other.^{11,12} These studies have supported the view that when we observe others' actions, observed action is automatically simulated and matched with internal motor representation and could even be imitated unconsciously (Chameleon effect).^{12,13} These externally triggered motor representations are then used to understand, learn, and reproduce the observed behavior.¹⁴ Therefore, for learning and acquiring new skills, the process of action perception is as important as that of motor execution.

Passive viewing of biological motions has been known to activate the superior temporal sulcus (STS),¹⁵ and the STS has been suggested to have a more extended function in social cognition such as detecting intention of

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others.^{16,17} Kim et al¹⁸ reported that schizophrenia patients were impaired in the perception of biological motion, and they predicted that impaired biological motion processing arises from functional deficit in the STS. Although the STS is a central node of processing biological motion, passive viewing of biological motion has consistently activated the posterior temporal-occipital cortex including the body-selective extrastriate body area (EBA)¹⁹ in close proximity to the STS.²⁰ Originally, the EBA was identified as an area that responds selectively to static human bodies and body parts.¹⁹ In biological motion tasks, low-level visual stimuli such as random moving dots have been used as control task, which make it difficult to clarify whether the EBA is only involved in body-sensitive early visual processing or is participant as a part of a system for inferring the action and intention of others like the STS. However, recent studies have suggested an extended role for the EBA, involving not only static visual perception of body parts but also the planning, imagination, and execution of actions.^{21,22} In addition, we have shown that sports-related context-congruent actions produced greater activation in the EBA, along with the STS, than context-incongruent actions.²³ Compared with frontal or limbic areas, the posterior temporal-occipital or temporal-parietal cortex has received relatively little attention in the field of schizophrenia research,²⁴ and functional abnormality of the EBA in schizophrenia has yet to be investigated. We hypothesized that patients with schizophrenia would show diminished activation in the EBA, along with the STS, in response to sports-related context-congruent actions.

Methods

Participants Twelve patients with schizophrenia (6 men and 6 women, mean age: 31.8 ± 7.2 [SD] years) were studied. Diagnoses were based on the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Axis I Disorders. All patients were attending the day hospital unit of Asai Hospital. Exclusion criteria were current or past substance abuse and a history of alcohol-related problems, mood disorder, or organic brain disease. The mean illness duration was 9.8 ± 6.9 years. All patients received antipsychotics (mean chlorpromazine equivalent daily dosage = 641.6 ± 471.2 mg).^{25,26} Clinical symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.²⁷ Mean total scores of PANSS and subscale (positive scale, negative scale, and general psychopathology scale) were 69.8 ± 13.6 , 14.3 ± 4.0 , 19.7 ± 4.7 , and 35.8 ± 6.4 , respectively. The ratings were reviewed by trained senior psychiatrists, H.T. and T.S., after the patient interviews, and disagreements were resolved by consensus; consensus ratings were used in this study. Twelve age-sex-matched normal controls (6 men and 6 women, mean age 29.4 ± 4.5 years) were recruited from the sur-

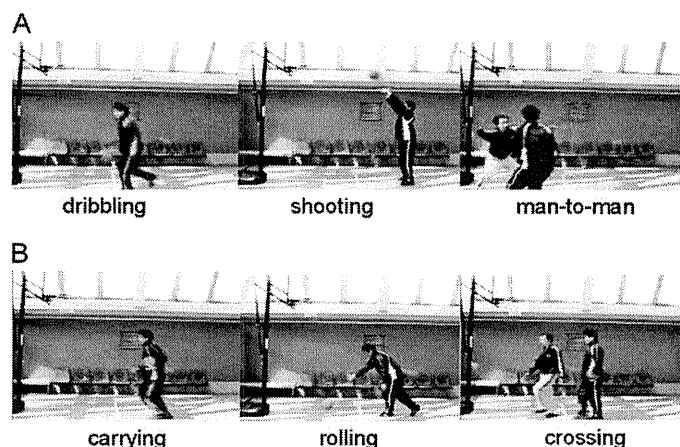


Fig. 1. Sample of Still Frames From Video Clips. A, Basketball-related motions; B, basketball-unrelated motions.

rounding community. The candidates were carefully screened, and standardized interviews were conducted by H.T. and T.S.. They did not meet criteria for any psychiatric disorders. None of the controls were taking alcohol or medication at the time, nor did they have a history of psychiatric disorder, significant physical illness, neurological disorder, or alcohol or drug dependence. All subjects were right-handed, and they all underwent a magnetic resonance imaging (MRI) to rule out cerebral anatomic abnormalities. All subjects had achieved an educational level of high school or higher. All of them had the experience of playing basketball in elementary school or junior high school, but they had little opportunity, if any, to play basketball thereafter. After complete explanation of the study, written informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Asai Hospital.

Materials

We employed the same visual stimuli as in the previous report where healthy volunteers were studied. The stimuli were designed to activate the EBA by sports-related actions.²³ Two types of video clips were provided (basketball-related motions [BRM] and basketball-unrelated motions [BUM]). Examples of the video clips are shown in figure 1. BRM consisted of 3 types of scenes (player shooting a free throw, player dribbling, 2 players performing man-to-man defense/offense). BUM also consisted of 3 types of scenes (player rolling a basketball, player carrying a basketball, and one person crossing in front of another without interaction). In order to make BRM and BUM as similar as possible, all players in the video clips performed in front of a basket hoop on a basketball court, and the number of persons, objects, motion direction, and speed were matched, ie, rolling a basketball, carrying a basketball, and crossing in front of another without interaction corresponded to shooting a free throw, dribbling, and man-to-man defense,

respectively. The video clips were projected via computer onto a screen mounted on a head coil. The subjects were instructed to pay attention to the video clips and to press a selection button with the right index finger when they watched the free throw scene and the basketball-rolling scene, indicating that they had paid attention to them. The experimental design consisted of 5 blocks for each of the 2 conditions (BRM and BUM) interleaved with 20-second rest periods. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In the BRM and BUM 24-second blocks, 3 scenes were presented twice for 4 seconds each.

Image Acquisition

Images were acquired with a 1.5-T Signa system (General Electric, Milwaukee, WI). Functional images of 115 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; echo time (TE), 50 ms; repetition time (TR), 4 sec; matrix, 64 × 64; field of view, 24 × 24 cm). High-resolution, T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices; 3D Spoiled-Grass sequence; slice thickness, 1.5 mm; TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; field of view, 25 × 25 cm).

Analysis of Functional Imaging Data

Data analysis was performed with SPM02 (Wellcome Department of Cognitive Neurology, London, UK). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the Montreal Neurological Institute template. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (full width at half maximum of 8 mm). Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of the *t* statistic were calculated on a voxel-by-voxel basis.

To examine possible group differences in response to BUM (baseline), we conducted a 2-sample *t* test of BUM contrast. To assess the specific condition effect, we used the contrasts of BRM minus BUM. A random-effects model was implemented for group analysis. A 1-sample *t* test was applied to determine group activation for the contrasts of BRM minus BUM. Between-group comparison of BRM minus BUM contrast was performed with a 2-sample *t* test. We used SPM's small volume correction to correct for multiple testing in regions about which we had a priori hypotheses. These a priori volumes of interest (VOIs) included the EBA (inferior temporal cortex) and STS (superior temporal

cortex). VOIs were defined by standardized VOI templates implemented in brain atlas software.²⁸ Significant differences surviving this correction at $P < .05$ were determined as were activations outside regions of interest surviving a threshold of $P < .001$, uncorrected, with an extent threshold of 10 contiguous voxels.

We conducted regression analyses to demonstrate a link between regional brain activities with the patients' demographics. Using the demographic data (age, duration of illness, chlorpromazine equivalent daily dosage, and PANSS scores) for each subject as covariates, regression analyses with the BRM minus BUM contrasts and the covariates were performed at the second level. The same threshold as used in the between-group comparison was applied. To confine the regions where significant group differences were observed, we created masks of group differences of the BRM minus BUM contrast from the 2-sample *t* test (threshold at $P < .05$, uncorrected), and these masks were applied inclusively. Using the effect sizes, representing the percent signal changes, of the BRM minus BUM contrasts at the peak coordinates uncovered in the regression analyses, we plotted the functional MRI (fMRI) signal changes and PANSS scores.

Results

Behavioral Data

All patients and controls paid attention to the video clips and pressed the button appropriately (accuracy was virtually 100%).

fMRI Results

In the control group, BRM minus BUM condition produced activations in the bilateral posterior temporal-occipital cortex including the bilateral EBA ($x = 58$, $y = -60$, $z = 2$; $t = 4.86$), middle temporal ($x = 54$, $y = -66$, $z = -12$; $t = 8.38$), right STS ($x = 56$, $y = -22$, $z = -2$; $t = 6.58$), bilateral premotor cortex ($x = -48$, $y = -4$, $z = 40$; $t = 4.94$), and bilateral inferior parietal lobules ($x = -34$, $y = -50$, $z = 54$; $t = 7.25$) (coordinates and *t* score refer to the peak of each brain region). In the patient group, BRM minus BUM condition produced activations in the left lingual gyrus ($x = -6$, $y = 92$, $z = 0$; $t = 6.52$), right prefrontal cortex ($x = 36$, $y = 52$, $z = 14$; $t = 5.66$), and right premotor cortex ($x = 36$, $y = -2$, $z = 54$; $t = 4.52$).

A 2-sample *t* test revealed no significant differences (threshold at $P < .001$, uncorrected) in the activations by BUM between controls and patients. Group comparison of the BRM minus BUM contrast showed that patients demonstrated significantly less activation in the bilateral EBA, bilateral parahippocampal gyrus, right STS, right temporal pole, right lingual gyrus, and globus pallidus (table 1 and figure 2). The activations in a priori regions (EBA and STS) survived a threshold of $P < .05$

Table 1. Regions showing diminished activation in response to BRM-BUM condition in 12 patients with schizophrenia compared with 12 controls

Brain regions	R/L	MNI coordinates			BA	<i>t</i> value	voxels
		<i>x</i>	<i>y</i>	<i>z</i>			
EBA (MTG)*	L	-40	-60	-4	37	5.37	106
EBA (MTG)*	R	52	-68	6	37	5.08	74
STS (STG)*	R	54	-22	0	21, 22	6.61	100
Temporal pole (STG)	R	40	10	-28	38	4.04	27
Parahippocampal gyrus	R	26	-26	-20	35	5.92	111
Parahippocampal gyrus	R	18	-38	-4	30	5.12	25
Parahippocampal gyrus	L	-28	-44	-6	19, 37	4.08	48
Lingual gyrus	R	6	-92	-10	17	4.28	21
Globus pallidus	R	16	-10	-2		4.12	21

Coordinates and *t* value refer to the peak of each brain region. MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right; MTG, middle temporal gyrus; STG, superior temporal gyrus BRM, basketball-related motions; BOM, basketball-unrelated motions; EBA, extrastriate body area; STS, superior temporal sulcus. All values, *P* < .001, uncorrected. **P* < .05, corrected for multiple comparisons across a small volume of interest.

corrected for multiple comparisons across a small VOI. No significantly greater activation was identified in patients in the group comparison of the BRM minus BUM contrast.

Regression analysis revealed negative linear correlations between the negative scale score of PANSS and the degree of activation in the left EBA (*x* = -58, *y* = -58, *z* = -6; *t* = 7.01) in BRM minus BUM contrast (figure 3). Scores of the general psychopathology scale were also negatively correlated with the degree of activation in the left EBA (*x* = -58, *y* = -56, *z* = -6; *t* = 5.81) (figure 3). These correlations in a priori regions (EBA) survived a threshold of *P* < .05 corrected for multiple comparisons across a small VOI. There was no correlation between the positive scale score and regional brain activation. Regression analysis revealed that none of age, duration of illness, or chlorpromazine equivalent daily dosage had a relation with regional brain activation.

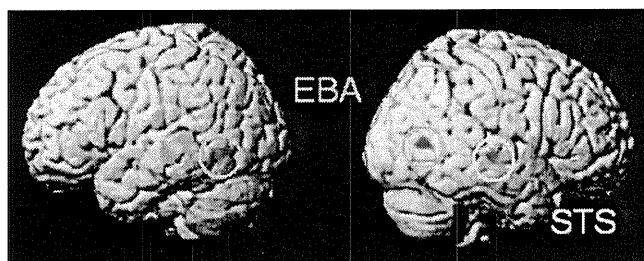


Fig. 2. Images Showing the Brain Area of Diminished Activations in Response to Basketball-Related Motions (BRM) Relative to Basketball-Unrelated Motions (BUM) Condition in 12 Patients With Schizophrenia Compared With 12 Normal Controls. Diminished activations in the bilateral extrastriate body area (EBA), right superior temporal sulcus (STS), and right temporal pole are shown.

Discussion

This study demonstrated that patients with schizophrenia showed diminished brain activations during observation of context-congruent actions in the EBA, along with the STS. The coordinates of the EBA were in good agreement with the previous literature (reviewed in Arzy et al²⁹). The lesser activation of the STS in the patients was fairly predicted because previous psychological study has shown the impairment of biological motion perception in schizophrenia, which has been thought to be attributable to dysfunction of the STS.¹⁸ The STS is located at a convergence zone for multimodal signals including limbic information,³⁰ and it has been suggested to be involved not only in the perception of biological motion but also in a more extended function of social cognition such as understating others' intention.^{16,17} Dysfunctional STS might contribute to a difficulty in understanding intentional actions and behavior of agents in schizophrenia.³¹

The novel finding in this study was that the patients showed diminished EBA activation in response to context-congruent actions despite the fact that the patients comprehended explicit information of body movement (and basketball rules) similar to controls. This implies that the patients might not have processed implicit information carried by body movements as much as controls, but it is very difficult to quantify such implicit information and complex EBA function in a limited MRI environment and in a limited time period. Interestingly, PANSS score, instead of performance during fMRI scans, was directly linked to EBA activation in patients. That is, the less EBA activation was, the more severe the symptoms (negative and general psychopathology) in the patients were. The EBA was first identified as an area that responds selectively to static human bodies.¹⁹ Recent

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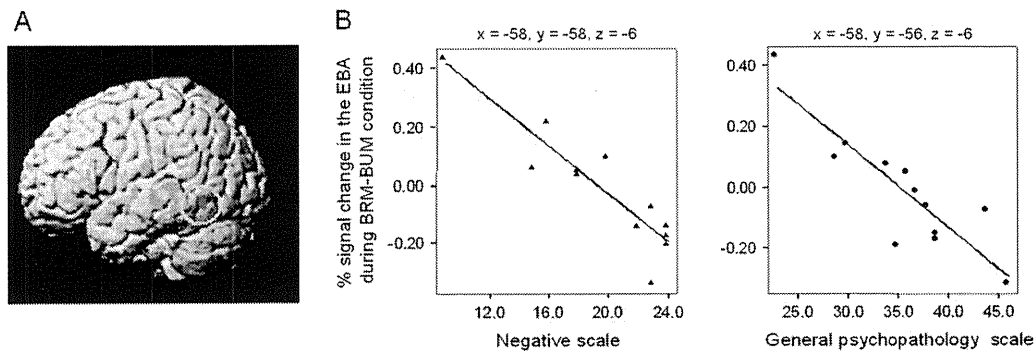


Fig. 3. Negative Correlations Between Positive and Negative Syndrome Scale (PANSS) Scores and the Degree of Activation in the Extrastriate Body area (EBA). A, Images showing negative correlation between negative scale scores and the degree of activation in the left EBA in basketball-related motions-basketball-unrelated motions (BRM-BUM) contrast. Scores of general psychopathology scale were also negatively correlated with the degree of activation in the left EBA in BRM-BUM contrast, yielding images identical to A. B, Plots and regression lines of negative correlations between PANSS scores and the degree of activation in the left EBA. The degrees of activations in the EBA were negatively correlated with the scores of negative scale ($r = -0.91$, $df = 10$; $P < .001$) and general psychopathology scale ($r = -0.88$, $df = 10$; $P < .001$).

studies have suggested that the EBA is also directly involved in representing the dynamic aspects of human motions as part of a system for inferring the intention of others.³² Jackson *et al.*²² reported that, compared with observation of actions, EBA activation was enhanced during imitation. Furthermore, the motivation to act has been shown to modulate EBA activity.³³ These studies proposed an extended role for the EBA, involving the planning, execution, and imagination of actions. Our previous report that using the current task in healthy volunteers was in favor of this view,²³ suggesting that the EBA might contribute to the understanding of actions and intention of others through the mechanism of observed action being automatically represented and simulated.^{14,32}

Empirical studies have shown that schizophrenia patients have difficulty in representing motor actions internally.^{34,35} The diminished EBA activation in patients suggests that internal representation of the dynamic aspects of human motions is impaired. Motor representation is associated with understanding and rehearsing observed behavior.¹⁴ In fact, recent studies demonstrated that motor representation is highly involved in skill learning and motor rehabilitation.^{36,37} Consequently, the deficit in the EBA in schizophrenia could lead to difficulties in learning and reproducing new skills in addition to impairment in understanding others' actions.

The present study has several limitations. First, we examined only patients with chronic schizophrenia with long-term antipsychotic medication because our primary interest was the possible role of sports participation/observation in the management of chronic schizophrenia and comorbid metabolic disturbances partly due to antipsychotic medication. Medication possibly affects neural activation, but regression analysis revealed that chlorpromazine equivalent daily dosage has no relation with regional brain activation, and expression of dopamine D2 receptors in the posterior temporal-occipital cortex is extremely low.³⁸ Second, our task

was not a behaviorally/cognitively demanding task leading to lack of dispersion in behavioral data (100% accuracy for both control and patient groups). Using a behaviorally/cognitively demanding task would require us to include only patients with psychiatric symptoms and cognitive impairments mild enough to undergo the imaging procedure and comply with the demanding task. However, the target patients of rehabilitation and management of comorbid metabolic disturbances in a day hospital have considerable behavioral and cognitive disturbances, which make it difficult to obtain reliable self-reported data of complex and subtle functions. Therefore, we employed the current task, aiming to examine patients with chronic schizophrenia in a real-world setting. From these limitations, it must be emphasized that any generalization of our findings to patients with first episode or nondeficit patients needs to be approached with caution.

In conclusion, chronic schizophrenia patients demonstrated diminished activation in the EBA in response to sports-related actions. Dysfunction of the EBA might reflect impairment of representation of dynamic aspects of human actions and might lead to impairments in simulation, learning, and execution of actions in schizophrenia. Furthermore, these impairments might lead to difficulty in understanding others' actions, interpersonal communication, body awareness, and overall physical activity manifested as negative symptoms and general psychopathology symptoms. The results of this study seem to have some important clinical implications for the management of chronic schizophrenia and merit further investigation in terms of the role of sports participation/observation in the rehabilitation for chronic schizophrenia and their effects on EBA function.

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Contribution of Dopamine D1 and D2 Receptors to Amygdala Activity in Human

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Several animal studies have demonstrated functional roles of dopamine (DA) D1 and D2 receptors in amygdala activity. However, the contribution of DA D1 and D2 receptors to amygdala response induced by affective stimuli in human is unknown. To investigate the contribution of DA receptor subtypes to amygdala reactivity in human, we conducted a multimodal *in vivo* neuroimaging study in which DA D1 and D2 receptor bindings in the amygdala were measured with positron emission tomography (PET), and amygdala response induced by fearful faces was assessed by functional magnetic resonance imaging (fMRI) in healthy volunteers. We used multimodality voxelwise correlation analysis between fMRI signal and DA receptor binding measured by PET. DA D1 binding in the amygdala was positively correlated with amygdala signal change in response to fearful faces, but DA D2 binding in the amygdala was not related to amygdala signal change. DA D1 receptors might play a major role in enhancing amygdala response when sensory inputs are affective.

Introduction

The amygdala plays 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 both dopamine (DA) D1 and D2 receptors are expressed in this region (Ito et al., 2008), although the latter exhibit lower expression (Scibilia et al., 1992). DA release in the amygdala is increased in response to stress (Inglis and Moghaddam, 1999). It has been shown in animal studies that DA potentiates the response of the amygdala by augmenting excitatory sensory input and attenuating inhibitory prefrontal input to the amygdala (Rosenkranz and Grace, 2002). Systemic and local applications into the amygdala of D1 agonist and antagonist are known to potentiate and decrease fear response in animals, respectively. 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 Pezze and Feldon, 2004; de la Mora et al., 2009).

A human functional magnetic resonance imaging (fMRI) study reported that dopaminergic drug therapy such as levo-

dopa or DA agonists partially restored amygdala response due to emotional task in Parkinson's disease patients who showed no significant amygdala response 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-[¹⁸F]fluoro-L-DOPA positron emission tomography (PET), was positively correlated with functional magnetic resonance imaging (fMRI) signal changes in amygdala. However, the contribution of DA D1 and D2 receptors to amygdala response induced by affective stimuli is unknown in human. To investigate the relation between amygdala reactivity and dopamine receptor subtype, we conducted a multimodal *in vivo* neuroimaging study in which DA D1 and D2 receptor bindings in the amygdala were measured with PET, and amygdala response by novel faces with either neutral or fearful expression was assessed with fMRI. Based on animal pharmacological studies, we hypothesized that D1, but not D2 receptors, would predict amygdala response.

Materials and Methods

Subjects

Twenty-one male volunteers [mean age 23.1 ± (SD) 3.6 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. All subjects were right-handed according to the Edinburgh Handedness Inventory. All subjects underwent MRI to rule out cerebral anatomic abnormalities. After complete explanation of the study,

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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.

fMRI procedure

Stimulus materials were taken from the Karolinska Directed Emotional Faces (KDEF) (Lundqvist et al., 1998). Thirty neutral and 30 fear faces were used, with half of them being male faces. The pictures were projected via a computer and a telephoto lens onto a screen mounted on a head-coil. The experimental design consisted of 5 blocks for each of the 2 conditions (neutral, fear) interleaved with 21 s rest periods. The order of presentation for the 2 conditions (neutral and fear) was randomized. During the baseline condition, subjects viewed a crosshair pattern projected to the center of the screen. In each 21 s block, 6 different faces of the same emotional class were presented for 3.5 s each. During the scans, the subjects were instructed to judge the gender of each face using selection buttons.

fMRI scanning

The images were acquired with a 3.0 Tesla Excite system (General Electric). Functional images of 126 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to the blood oxygenation level-dependent (BOLD) contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; echo time, 50 ms; repetition time, 3500 ms; matrix, 64 × 64; field of view, 24 × 24 cm).

Analysis of fMRI data

Data analysis was performed with the statistical parametric mapping software package (SPM2) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (MathWorks). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans had a resolution of 2 × 2 × 2 mm³. Functional images were spatially smoothed with a three-dimensional isotropic Gaussian kernel (full-width at half-maximum of 8 mm). Low-frequency noise was removed by applying a high-pass filter (cutoff period = 128 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of *t*-statistic were calculated on a voxel-by-voxel basis.

We assessed the contrasts of fear and neutral minus baseline (F&N-B). A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. The contrast images were obtained from single-subject analysis and entered into the group analysis. A one-sample *t* test was applied to determine group response for each effect. Significant amygdala activations were identified if they reached the extent threshold of $p < 0.05$ corrected for multiple comparisons, with a height threshold of $p < 0.001$, uncorrected.

PET scanning

After the fMRI session, each participant underwent PET scanning. The interval between fMRI session and PET scan was 3–5 h. 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. For evaluation of D1 receptors, a bolus of 219.7 ± 6.9 MBq of [¹¹C]SCH23390 with specific radioactivities (95.7 ± 35.5 GBq/μmol) was injected intravenously from the antecubital vein with a 20 ml saline flush. For evaluation of extrastriatal DA D2 receptors, a bolus of 218.1 ± 14.7 MBq of [¹¹C]FLB457 with high specific radioactivities (221.6 ± 94.9 GBq/μmol) was injected in the same way. Dynamic scans were performed for 60 min for [¹¹C]SCH23390 and 90 min for [¹¹C]FLB457 immediately after the injection. 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; and number of excitations, 1).

Quantification of DA D1 and D2 receptors

Quantitative analysis was performed using the three-parameter simplified reference tissue model (Lammertsma and Hume, 1996; Olsson et al., 1999). The cerebellum was used as a reference region because it has been shown to be almost devoid of DA D1 and D2 receptors (Farde et al., 1987; Olsson et al., 1999; 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: $BP_{ND} = k_3/k_4 = f_2 B_{max}/\{K_d [1 + \sum_i F_i/K_{di}]\}$, 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 dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996). Tissue concentrations of the radioactivities of [¹¹C]SCH23390 and [¹¹C]FLB457 were obtained from regions of interest (ROIs) defined on PET images of summated activity for 60 min and 90 min, respectively, with reference to the individual MRIs coregistered on summated PET images and the brain atlas. Given our hypothesis of amygdala activation during viewing novel neutral and fearful faces, ROIs were set on the bilateral amygdala. The method for defining the boundaries of the amygdala was adapted from previously described methods (Kates et al., 1997; Convit et al., 1999). In short, the amygdala ROIs consisted of three axial slices. The anterior and posterior boundaries were identified at the level of the optic chiasm and the temporal horn of the lateral ventricle, respectively. The superior and inferior-lateral boundaries were identified at the level of the mammalian body and the temporal lobe white matter and extension of the temporal horn, respectively. We also created parametric images of BP_{ND} using the basis function method (Gunn et al., 1997) to conduct voxelwise SPM analysis in addition to ROI analysis.

Statistical analysis

ROI correlation analysis. Estimates of percentage signal change of fear vs baseline condition were extracted from the amygdala for each participant using the MarsBaR toolbox (Brett et al., 2002). The bilateral amygdala ROIs were defined from the WFU-Pickatlas SPM tool (Maldjian et al., 2003) with the aal atlas (Tzourio-Mazoyer et al., 2002). Correlation between BP_{ND} of [¹¹C]SCH23390 and [¹¹C]FLB457 in the bilateral amygdala and bilateral amygdala fMRI signal change were calculated using SPSS.

Confirmatory SPM correlation analysis. Parametric images of BP_{ND} of [¹¹C]SCH23390 and [¹¹C]FLB457 were analyzed using SPM2. Exactly the same image preprocessings of normalization and smoothing that were used in fMRI data analysis were applied to parametric images of BP_{ND}. To conduct multimodality voxelwise correlation analysis between the BOLD signal and DA receptor binding, we used the biological parametric mapping toolbox for SPM (Casanova et al., 2007). Significant clusters were identified if they reached the extent threshold of $p < 0.05$ corrected for multiple comparisons, with a height threshold of $R > 0.6$ ($p < 0.003$ uncorrected).

Results

Since the face pictures consisted of Caucasian faces (racial out-group), even novel neutral faces produced amygdala response in several participants (Hart et al., 2000; Schwartz et al., 2003), leading to a blunted contrast of fear minus neutral. Therefore, we combined neutral and fear conditions and used F&N-B contrast for analyses. Group analysis of F&N-B contrast revealed significant bilateral amygdala responses [right amygdala (26, 0, -26), $t = 4.43$, 93 voxels, left amygdala (-20, -2, -26), $Z = 4.96$, 101

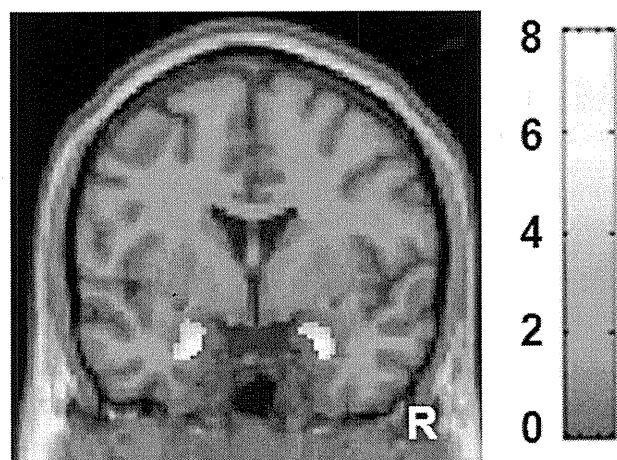


Figure 1. Images showing brain response induced by fear and neutral minus baseline condition. Bilateral amygdala responses are shown. The bar shows the range of the t -value. R indicates right.

voxels] (Fig. 1). The mean BP_{ND} of [^{11}C]SCH23390 in the right and left amygdala were 0.38 ± 0.08 and 0.39 ± 0.11 , respectively. The mean BP_{ND} of [^{11}C]FLB457 in the right and left amygdala were 2.49 ± 0.50 and 2.50 ± 0.44 , respectively.

Correlation analysis of biological parametric mapping revealed that the BP_{ND} value of [^{11}C]SCH23390 in the right amygdala was positively correlated with the BOLD signals in the right amygdala of F&N-B contrast [peak (28, 2, -28), 24 voxels] (Fig. 2A). ROIs analysis also revealed a similar significant correlation ($r = 0.59$, $p = 0.005$) in the right amygdala (Fig. 2B), but not in the left amygdala ($r = 0.18$, $p = 0.43$). According to biological parametric mapping analysis, the BP_{ND} value of [^{11}C]FLB457 in the amygdala was not correlated with BOLD signals in the amygdala of F&N-B contrast. ROIs analysis showed that right and left amygdala D2 binding was not correlated with the BOLD signals in the right ($r = 0.26$, $p = 0.27$) and left amygdala ($r = 0.28$, $p = 0.23$), respectively. Both biological parametric mapping analysis and ROIs analysis showed that D1 binding in the right and left amygdala was not correlated with D2 binding in the right ($r = 0.24$, $p = 0.30$) and left amygdala ($r = 0.16$, $p = 0.49$), respectively. We used anatomically defined ROIs of the amygdala rather than functionally defined ROIs in the ROI correlation analysis because it is difficult to place functionally defined ROIs on individual PET data. Anatomically defined ROIs of the amygdala were larger than functionally defined amygdala ROIs. This fact was advantageous in increasing the signal-to-noise ratio in the PET analysis, but led to blunted BOLD signal changes in the amygdala. However, BOLD signal changes derived from both ROI methods were highly correlated with each other. For example, very high correlation ($r = 0.80$, $p < 0.001$) was observed in the right amygdala. Thus, regardless of ROI definition method, we obtained similar results from ROI correlation analyses between BOLD signal changes and DA receptor binding in the amygdala.

Discussion

Using a multimodality *in vivo* neuroimaging approach, we first directly compared amygdala DA D1 and D2 receptor bindings, indices of receptor availability, with amygdala response evoked by novel or fearful stimuli in human. We found that DA D1 receptors, but not D2 receptors, predicted amygdala response induced by novel facial stimuli with either neutral or fearful ex-

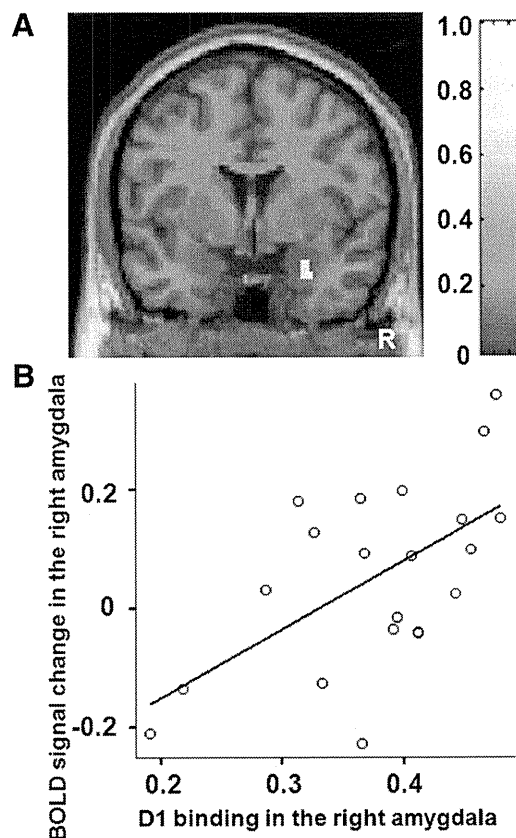


Figure 2. A, SPM correlation analysis revealed significant positive linear correlations between D1 binding in the right amygdala and right amygdala signal change. The bar shows the range of the correlation coefficient. B, ROI correlation analysis also revealed similar correlations. R indicates right.

pression. Our findings broaden our knowledge about dopaminergic transmission in amygdala response beyond the recent study (Kienast et al., 2008) that elucidated the relation between presynaptic dopamine synthesis and amygdala reactivity.

Human neuroimaging studies reported that DA potentiated amygdala response evoked by affective stimuli (Hariri et al., 2002; Tessitore et al., 2002). In rat studies, Rosenkranz and Grace (2002) demonstrated that DA enhances the response of the amygdala by augmenting excitatory sensory input via DA D2 receptor stimulation and attenuating inhibitory prefrontal input to the amygdala through DA D1 receptor stimulation. More recently, it was demonstrated that both D1 and D2 receptor stimulations directly enhanced the excitability of amygdala projection neurons via postsynaptic mechanism (Rosenkranz and Grace, 2002; Kröner et al., 2005; 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 DA D1 and D2 receptors (Rosenkranz and Grace, 1999). It has been shown that DA and D1 receptor stimulation augments interneuron excitability and increases the frequency of IPSC in amygdala projection neurons (Kröner et al., 2005). This is a counterintuitive result, considering the fact that DA disinhibits amygdala response *in vivo*. However, Marowsky et al. (2005) found that a subpopulation of amygdala interneurons (paracapsular intercalated cells), located between the major input and output stations of amygdala, is suppressed by DA through D1 receptor stimulation. DA D2 receptors also play a role in disinhibiting amygdala response by decreasing inhibi-

tion onto projection neurons and increasing inhibition onto interneurons (Bissière et al., 2003).

Although detailed examination of subnuclei of the amygdala is difficult in this imaging method, the dorsal portion of the amygdala roughly corresponds to the central nuclei of amygdala (CeA) and the ventral portion of the amygdala corresponds to the basolateral nuclei of amygdala (BLA) and intercalated cell masses (ICM) (Whalen et al., 2009). The amygdala clusters identified both in fMRI task effect analysis and in correlation analysis between D1 binding and amygdala reactivity were located in the ventral portion of the amygdala. Thus, our findings seem to mainly reflect BLA and ICM properties. It is worth mentioning that the highest density of D1 receptors within the amygdala was found in the ICM, followed by BLA, and the expression of D1 receptors is low in CeA (de la Mora et al., 2009; Muly et al., 2009). In contrast, D2 receptors are mainly distributed in CeA (de la Mora et al., 2009). Both D1 and D2 receptors are expressed both postsynaptically in dendrites and presynaptically in axon terminals (Pinto and Sesack, 2008; Muller et al., 2009; Muly et al., 2009), but D1 receptors in BLA are mainly expressed in the dendrites, indicating that DA directly modulates the excitability of BLA projection neurons and interneurons. At the same time, DA also acts on presynaptic D1 receptors to increase the probability of neurotransmitter release from glutamatergic terminals (Muly et al., 2009). Thus, the net DA effect on D1 receptors in the amygdala is a complex mixture of post- and presynaptic actions at several sites.

Although both DA D1 and D2 receptors contribute to potentiating amygdala response via various mechanisms as described above, our finding suggested that DA D1 receptors play a major role in the overall potentiation of amygdala response. At a behavioral level, previous animal studies repeatedly reported that D1 agonist and antagonist applications into the amygdala potentiated and decreased fear response, respectively. However, the effects of D2 agonist/antagonist on fear response have not been well established (Pezze and Feldon, 2004; de la Mora et al., 2009). Thus, the current 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 system neuroscience. However, this study has several limitations. First, current PET techniques for human do not have enough spatial resolution to distinguish subnuclei of the amygdala. Although analysis of parametric images of BP_{ND} has become well established (Gunn et al., 1997) and is used in many [¹¹C]SCH23390 and [¹¹C]FLB457 studies (Cervenka et al., 2006; Takahashi et al., 2008; Karlsson et al., 2009; McNab et al., 2009), a very small region or a single voxel is susceptible to partial volume effect. Thus, it is recommended that parametric image analysis should be used in combination with ROI analysis. At the same time, current results merit further investigation with a higher resolution PET scanner. Second, PET imaging cannot tell us the exact location of DA receptors expressed in projection neurons and interneurons. Future animal studies or *in vitro* studies would complement our findings to determine which D1 receptor-mediated mechanism is most responsible for the overall amygdala response. Third, differences in DA receptor occupancies by endogenous DA might affect BP, leading to different excitabilities of neurons. It is known that BP of [¹¹C]SCH23390 is not sensitive to competitive endogenous dopamine even if massive dopamine is released by amphetamine (Abi-Dargham et al., 1999; Chou et al., 1999). However, it is possible that differences in receptor affinity might contribute to differences in DA receptor

occupancies, although Farde et al. (1995) reported that variability in D2 receptor affinity is smaller than that in D2 receptor density. Finally, gender and race effects might also be possible. Any generalization should be approached with caution. Notwithstanding these limitations, we expect our finding to contribute to a broadening of the knowledge of the molecular mechanism of functional abnormalities of the amygdala implicated in neuropsychiatric disorders such as schizophrenia (Takahashi et al., 2004), depression (Drevets, 2000) and Parkinson's disease (Tessitore et al., 2002).

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Dopamine D₁ 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 D₁ and D₂ receptors in the brain are associated with transformation of probabilities into decision weights in healthy volunteers. The binding of striatal D₁ receptors is negatively correlated with the degree of nonlinearity of weighting function. Individuals with lower striatal D₁ 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 D₁ and D₂ 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 D₁ receptors are preferentially stimulated by phasically released DA, whereas low-level baseline tonic DA release is enough for stimulating striatal D₂ 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 D₁ receptors might be more associated with individual differences than that of available D₂ receptors.

Materials and Methods

Subjects

Thirty-six healthy male volunteers (mean age \pm SD, 25.2 \pm 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 (\sim 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 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 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 (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 \pm SD, 24.7 \pm 3.8 years) was studied for both D₁ receptors and extrastriatal D₂ receptors. These 18 subjects came to the PET center twice, once each for the studies of [¹¹C]SCH23390 (*R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) and [¹¹C]FLB457 ((*S*)-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide). For evaluation of D₁ receptors, a bolus of 215.9 \pm 9.8 MBq of [¹¹C]SCH23390 with specific radioactivities (90.1 \pm 38.5 GBq/ μ mol) was injected intravenously from the antecubital vein with a 20 ml saline flush. The fact that [¹¹C]SCH23390 has high affinity for D₁ receptors (Ekelund et al., 2007), and that D₁ receptors are mod-

erately expressed in the extrastriatal regions (approximately one-fifth of striatal D₁ receptor density) (Ito et al., 2008) leads to good reproducibility of both striatal and extrastriatal [¹¹C]SCH23390 bindings (Hirvonen et al., 2001). Although [¹¹C]SCH23390 is a selective radioligand for D₁ receptors, it has some affinity for 5HT_{2A} receptors. However, 5HT_{2A} receptor density in the striatum is negligible compared with D₁ receptor density. 5HT_{2A} receptor density is never negligible in the extrastriatal regions. Although previous reports in the literature have indicated that [¹¹C]SCH23390 affinity for 5HT_{2A} receptors relative to D₁ receptors is negligible, a recent *in vivo* study reported that approximately one-fourth of the cortical signal of [¹¹C]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 D₂ receptors, a bolus of 218.3 ± 13.9 MBq of [¹¹C]FLB457 with high specific radioactivities (238.0 ± 100.8 GBq/μmol) was injected in the same way. [¹¹C]FLB457 has very high affinity for D₂ receptors. It is a selective radioligand for D₂ receptors and has good reproducibility of extrastriatal D₂ bindings (Sudo et al., 2001). Dynamic scans were performed for 60 min for [¹¹C]SCH23390 and 90 min for [¹¹C]FLB457 immediately after the injection. Although [¹¹C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated since the duration of the [¹¹C]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 D₂ 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 [¹¹C]raclopride with a specific radioactivity of 451.1 ± 154.6 GBq/μmol was injected similarly. [¹¹C]Raclopride is a selective radioligand for D₂ receptors, and has good reproducibility of striatal D₂ bindings (Volkow et al., 1993). Because the density of extrastriatal D₂ receptors is less than one-tenth of striatal D₂ receptors (Ito et al., 2008), [¹¹C]raclopride is suitable for the evaluation of striatal D₂ receptors, but not of extrastriatal D₂ receptors, due to its moderate affinity for D₂ 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 D₁ and D₂ receptors

Because one subject felt discomfort from the head fixation device during the [¹¹C]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 [¹¹C]SCH23390, [¹¹C]FLB457 and [¹¹C]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 D₁ 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: $BP_{ND} = k_3/k_4 = f_2 B_{max} / \{K_d [1 + \sum_i F_i / K_{di}]\}$, 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_{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

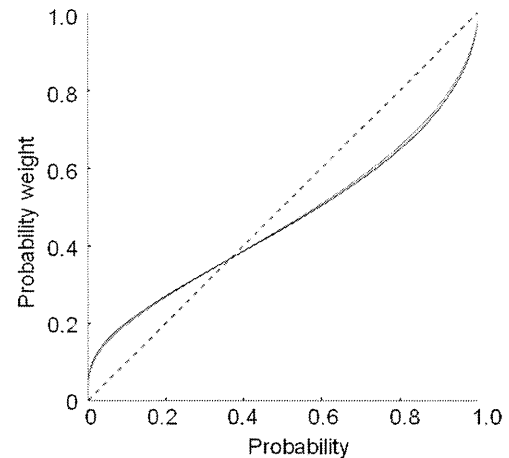


Figure 1. The fitted probability weighting function with the Prelec model. The red line represents the first group ($N = 18$ subjects) with D₁ receptors and extrastriatal D₂ receptors investigated. The black line is the second group ($N = 18$ subjects) whose striatal D₂ receptors were investigated.

[¹¹C]SCH23390, [¹¹C]FLB457 and [¹¹C]raclopride were obtained from anatomically defined ROIs. The individual MRIs were coregistered on [¹¹C]SCH23390, [¹¹C]FLB457 and [¹¹C]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_{ND} of [¹¹C]SCH23390, [¹¹C]FLB457 and [¹¹C]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 [¹¹C]SCH23390 and [¹¹C]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 [¹¹C]SCH23390 and [¹¹C]raclopride and behavioral parameters to control for the potential influence of smoking (number of cigarettes per day).

Results

In the first group, with D₁ receptors and extrastriatal D₂ 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 D₂ 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 sup-

plemental material), respectively. Normalized parametric images of BP_{ND} of [¹¹C]SCH23390, [¹¹C]raclopride and [¹¹C]FLB457 are shown in Figure 2A, B, and C, respectively. The mean BP_{ND} values of [¹¹C]SCH23390 in the caudate and putamen were 1.86 ± 0.24 and 2.01 ± 0.22 , and those of [¹¹C]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 D₁ 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. 3A). Independent ROI analyses revealed that D₁ receptor binding in the putamen showed a significant correlation with α (Fig. 3B; Table 1), and D₁ receptor binding in the caudate showed a trend level correlation with α (Table 1). That is, people with lower striatal D₁ 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 D₁ binding was not correlated with α . SPM and ROI analyses revealed that neither striatal nor extrastriatal D₂ receptor binding was correlated with α . None of [¹¹C]SCH23390, [¹¹C]FLB457 and [¹¹C]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 [¹¹C]SCH23390 and [¹¹C]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.

Discussion

We provided the first evidence of a relation between striatal D₁ 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 D₁ receptor binding showed more nonlinear probability weighting and more pronounced overestimation of low probabilities and underestimation of high probabilities. Low D₁ 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 D₁ receptors in the striatum. In contrast, low-level baseline tonic DA release is enough for stimulating D₂ receptors (Frank et al., 2007; Schultz, 2007). Therefore, the variability of D₂ receptor binding might have less impact on current behavioral task during which phasic DA release occurs in response to reward cue.

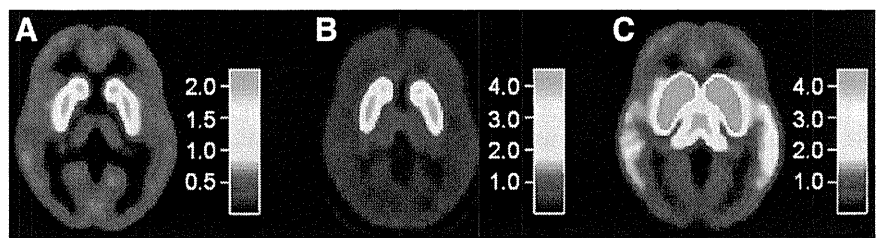


Figure 2. Maps of DA D₁ and D₂ BP, averaged across participants (axial slices at the level of Z = 0 of MNI coordinates). **A**, D₁ BP, measured with [¹¹C]SCH23390 (N = 18 subjects). **B**, Striatal D₂ BP, measured with [¹¹C]raclopride (N = 18 subjects). **C**, Extrastriatal D₂ BP, measured with [¹¹C]FLB457 (N = 17 subjects). Although [¹¹C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated because the duration of the [¹¹C]FLB457 PET study was not sufficient to obtain equilibrium in the striatum. The bar indicates the range of BP.

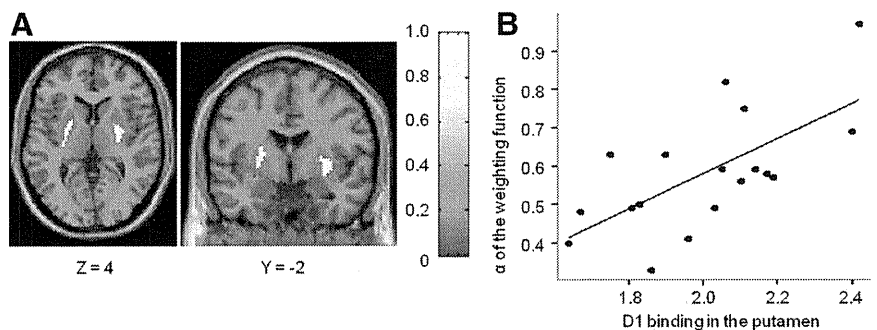


Figure 3. Correlation between nonlinearity of probabilities weighting and D₁ binding in the striatum (N = 18 subjects). **A**, Image showing regions of correlation between nonlinearity parameter of weighting function and D₁ binding in the striatum. The bar shows the range of the correlation coefficient. **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 [¹¹C]SCH23390 (N = 18 subjects) and [¹¹C]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. * $p < 0.01$.

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 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 (Tammenga 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 (Tammenga and Nestler, 2006). Animal studies demonstrated that stimulation of D₁ receptors by a selective agonist increased risky choice and blockade of D₁ receptors decreased risky choice in rats. Although D₂ agonist/antagonist showed similar actions, their effects were not as pronounced as those of D₁ agonist/antagonist (St Onge and Floresco, 2009). A human genetic study reported that variants of the gene for D₁ 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 D₁ 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 D₁ 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 D₂ 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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