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Science
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When Your Gain Is My Pain and Your Pain Is My Gain: Neural Correlates of Envy and Schadenfreude

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Science **323**, 937 (2009);
DOI: 10.1126/science.1165604

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

knockout mouse (*27*). [^{125}I]IAF photolabeling of liver homogenates from wild-type (WT) and sigma-1 receptor knockout (KO) mice indeed showed the absence of sigma-1 receptor (26 kD) in the KO samples (Fig. 3A). In WT neonatal cardiac myocytes, 100 μM DMT reversibly inhibited I_{Na} by 29 ± 3% (n = 7 WT myocytes), whereas I_{Na} was reduced by only 7 ± 2% (n = 7 KO myocytes) in KO myocytes (Fig. 3C, $P < 0.002$).

Both DMT and sigma receptor ligands influence animal behavior. DMT injection induces hypermobility in rodents concurrently treated with the monoamine oxidase inhibitor pargyline (*28*), and this action is not antagonized by blockers of dopamine or serotonin receptors, but is potently inhibited by haloperidol (*28*). Although haloperidol is thought to act in part through the dopamine D_2 receptor system, it is also a potent sigma-1 receptor agonist [sigma-1 inhibition constant (K_i) = 3 nM (*29*); sigma-2 K_i = 54 nM (*29*)] when inhibiting voltage-gated ion channels (*5*, *25*). Haloperidol reduces brain concentrations of DMT (*8*) and DMT inhibits haloperidol binding in brain tissue more robustly than the dopamine agonist apomorphine (*8*). On the basis of these findings, which were discovered before sigma receptor identification, DMT has been hypothesized to act through an unknown "hallucinogen" receptor (*8*). We confirmed results (*28*) that intraperitoneal (ip) administration of DMT (2 mg per kilogram of body weight) 2 hours after pargyline (75 mg/kg, ip) injection induced hypermobility in WT mice (7025 ± 524.1 cm, n = 12 WT mice) in an open-field assay. Identical drug treatments in sigma-1 receptor KO mice had no hypermobility action (2328 ± 322.9 cm, n = 12 KO mice, $P < 0.0001$; Fig. 4, A and B). This result is particularly important to our understanding of sigma-1 receptor biological function because the KO mice are viable and fertile (*27*). The sigma-1 receptor dependence of DMT-induced hypermobility parallels that induced by the sigma-1 receptor ligand (+)-SKF10047 in WT but not in KO mice (*27*). As a positive control, methamphetamine, which is thought to act through catecholaminergic systems, induced hypermobility in both WT and KO mice (3 mg/kg, ip, n = 6 mice; Fig. 4, B and C) with a reduced onset rate compared with that seen for DMT (Fig. 4, A and C). This indicates that behavioral actions of DMT depend on the sigma-1 receptor, which may provide an alternative research area for psychiatric disorders that have not been linked to dopamine or *N*-methyl-D-aspartate systems.

The binding, biochemical, physiological, and behavioral studies reported here all support the hypothesis that DMT acts as a ligand for the sigma-1 receptor. On the basis of our binding results and the sigma-1 receptor pharmacophore, endogenous trace amines and their *N*-methyl and *N,N*-dimethyl derivatives are likely to serve as endogenous sigma receptor regulators. Moreover, DMT, the only known mammalian *N,N*-dimethylated trace amine, can activate the sigma-1 receptor to modulate Na^+ channels. The recent discovery that the sigma-1 receptor functions as a molecular chaperone (*30*) may be relevant, because sigma-1 receptors, which are observed in the endoplasmic reticulum, associate with plasma membrane Kv 1.4 channels (*22*) and may serve as a molecular chaperone for ion channels. Furthermore, the behavioral effect of DMT may be due to activation or inhibition of sigma-1 receptor chaperone activity instead of, or in addition to, DMT/sigma-1 receptor modulation of ion channels. These studies thus suggest that this natural hallucinogen could exert its action by binding to sigma-1 receptors, which are abundant in the brain (*1*, *27*). This discovery may also extend to *N,N*-dimethylated neurotransmitters such as the psychoactive serotonin derivative *N,N*-dimethylserotonin (bufotenine), which has been found at elevated concentrations in the urine of schizophrenic patients (*10*). The finding that DMT and sigma-1 receptors act as a ligand-receptor pair provides a long-awaited connection that will enable researchers to elucidate the biological functions of both of these molecules.

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31. We thank the Corinna Burger laboratory for use of their mouse behavior equipment, and A. Paul and T. Mavlyutov for providing [^{125}I]IAF and [^{125}I]-IACoc, respectively. Supported by the Molecular and Cellular Pharmacology (MCP) Graduate Program training grant from NIH T32 GM06688 and by the NIH Ruth L. Kirschstein National Research Service Award (NRSA) (F31 DA022932) from the National Institute on Drug Abuse (to D.F.). This work was funded by NIH grants R01 MH065503 (to A.E.R.) and NS30016 (to M.B.J.).

Supporting Online Material

www.sciencemag.org/cgi/content/full/323/5916/934/DC1
Materials and Methods
Fig. S1 and scheme S2
References

18 September 2008; accepted 10 December 2008
10.1126/science.1166127

When Your Gain Is My Pain and Your Pain Is My Gain: Neural Correlates of Envy and Schadenfreude

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We often evaluate the self and others from social comparisons. We feel envy when the target person has superior and self-relevant characteristics. Schadenfreude occurs when envied persons fall from grace. To elucidate the neurocognitive mechanisms of envy and schadenfreude, we conducted two functional magnetic resonance imaging studies. In study one, the participants read information concerning target persons characterized by levels of possession and self-relevance of comparison domains. When the target person's possession was superior and self-relevant, stronger envy and stronger anterior cingulate cortex (ACC) activation were induced. In study two, stronger schadenfreude and stronger striatum activation were induced when misfortunes happened to envied persons. ACC activation in study one predicted ventral striatum activation in study two. Our findings document mechanisms of painful emotion, envy, and a rewarding reaction, schadenfreude.

Envy is one of the seven biblical sins, the Shakespearian "green-eyed monster," and what Bertrand Russell (*1*) called an unfortunate facet of human nature. It is an irrational, unpleasant feeling and a "painful emotion" (*2*) characterized by feelings of inferiority and resentment produced by an awareness of another's superior quality, achievement, or possessions (*3*). Understanding envy is important because of its broad implications, ranging from individual mat-

ters to social problems. It concerns personal life satisfaction (*4*), self-evaluation/maintenance (*5*), and economic and political issues (*6*–*8*). We judge objects more by comparison than by their intrinsic worth and value (*9*), and self-evaluations are often derived from social comparisons with people who are self-relevant, sharing similar attributes, characteristics, group memberships, and interests (for example, gender, age, and social class) (*10*).

When envy is evoked, we often have a desire to possess the same advantage or may wish that the other lacks it (*3*). When misfortune occurs to others, emotions can manifest themselves in several ways. We can sympathize and have feelings of concern and sorrow for the other person (*11*, *12*), but we can also experience schadenfreude, a rewarding feeling derived from another's misfortune (*13*). Schadenfreude is closely related to envy, and it is more likely to arise when misfortune happens to a person who is advantaged and self-relevant than to someone who is neither advantaged nor self-relevant (*13*–*15*).

We investigated the brain activation associated with envy and schadenfreude. We conducted two functional magnetic resonance imaging (fMRI) studies to test two complementary hypotheses. In the first study, we hypothesized that, not only the level of possession of the person we compare ourselves with, but also the self-relevance of the comparison domain affects brain activation associated with envy through social comparison. We usually have a positive self-concept, and we experience a feeling of discomfort when we perform in a way that violates this self-concept (*16*). The anterior cingulate cortex (ACC) is activated when this positive self-concept conflicts with external information (*17*, *18*). Bearing in mind that envy is a painful emotion, we hypothesized that envy activates the dorsal ACC (dACC), where cognitive conflicts (*19*) or social pain (*12*, *20*) are processed. We predicted that dACC activation is stronger when an envied person has superior and more self-relevant possessions. In the second study, we hypothesized that a misfortune happening to an envied person produces greater brain activation associated with schadenfreude than misfortune happening to a person who is not envied. Schadenfreude should activate the ventral striatum, a central node of reward processing.

Nineteen healthy volunteers [10 men and 9 women, mean age = 22.1 ± 1.4 (SD) years] participated in the two fMRI studies. We used a scenario method as in previous social affective neuroimaging studies (*21*, *22*). Each participant was presented with a scenario in which the protagonist (oneself) and three other target persons appeared. Materials were employed from an initial survey to validate our expected results (*23*). Before the fMRI scans, we asked the participants to read and understand the scenario thoroughly and to imagine the protagonist of the scenario as themselves. In study one, we aimed to determine the level of envy in terms of whether possessions of the target person were superior or not and whether domains of comparison were self-relevant or not. In short, for male participants, the protagonist of the scenario was male and average in terms of possessions such as ability, quality, and social status. Male student A shared similar attributes with the protagonist. He possessed superior quality and ability, and the domains of comparison were important and relevant to the protagonist [superior and high relevance (SpHi)]. Female student B had different attributes and background from the protagonist. She also possessed superior quality and ability, but the domains of comparison were neither important nor relevant to the protagonist [superior and low relevance (SpLo)]. Female student C had different attributes and background from the protagonist. She possessed mediocre quality and ability, and the domains of comparison were neither important nor relevant to the protagonist [average and low relevance (AvLo)]. The scenario for male participants and profiles of the persons are shown in the appendix in (*23*). The profiles of the three target persons and comparison domains are summarized in table S1, and a schematic depiction of the stimuli and design is shown in fig. S1. We performed event-related fMRI analysis with statistical parametric mapping 2 to examine activations in response to SpHi, SpLo, and AvLo. In study two, successive misfortunes happened to student A (SpHi) and student C (AvLo) in the scenario examining reaction in response to misfortunes happening to others. A list of misfortunes is provided in table S1, and a schematic depiction of the stimuli and design is shown in fig. S2. We analyzed neural responses to misfortunes on SpHi (MisSpHi) and AvLo (MisAvLo). After the scans, the participants rated each event presented in study one in terms of how much envy they felt for the three students (i.e., 1 = no envy, 6 = extremely envious). Similarly, the participants also reported the intensity of their pleasure (schadenfreude) (1 = no pleasure, 6 = extremely pleasant) in response to misfortunes happening to students A and C in study two. That is, they gave one envy score per domain per student in study one and one schadenfreude score per misfortune per student in study two.

The self-rating results of the participants in the fMRI study were comparable to the results obtained in the initial survey. The mean values of the ratings of envy for students A, B, and C were 4.0 ± 1.0, 2.1 ± 0.8, and 1.0 ± 0.0, respectively. The mean values of schadenfreude for students A and C were

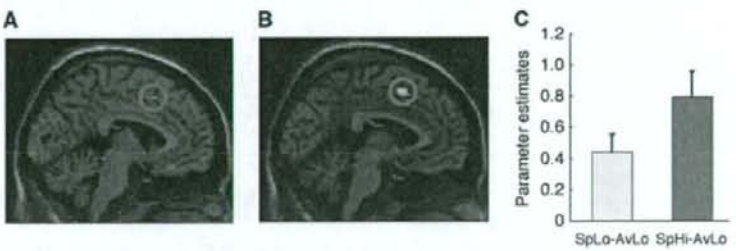

Fig. 1. Brain activation in dACC was modulated by relevance of comparison domain. Brain activations in response to **(A)** the SpLo minus AvLo condition and **(B)** the SpHi minus AvLo condition. **(C)** Mean for parameter estimates at the peak of dACC activation for SpHi-AvLo contrast (red) was greater than that for SpLo-AvLo contrast (yellow) ($t = 2.56$, $P = 0.02$). Error bars represent SE.

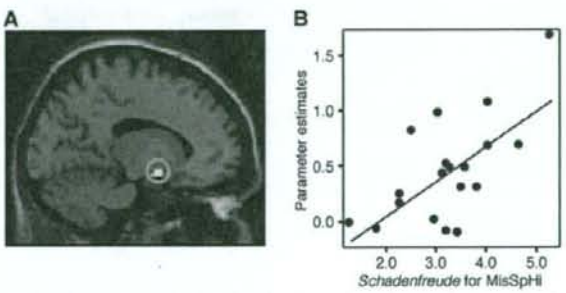

Fig. 2. Correlation between self-rating of schadenfreude and ventral striatum activation across participants. **(A)** Image showing correlation between mean rating of schadenfreude for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. **(B)** Plots and regression line of correlation ($r = 0.65$, $P = 0.002$) between schadenfreude and parameter estimates of the ventral striatum activation for MisSpHi-MisAvLo contrast at a peak voxel (−14, 2, −12).

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3.3 ± 1.0 and 1.0 ± 0.0, respectively. Self-rating scores of envy for student A were positively correlated with the magnitude of schadenfreude for student A (correlation coefficient $r = 0.50$, $P = 0.03$). Both SpHi-AvLo and SpLo-AvLo conditions produced activations in dACC, a region implicated in the processing of conflict or pain, but dACC activation was greater in the SpHi-AvLo condition ($x = -4$, $y = 8$, $z = 54$, z score = 4.07) than in the SpLo-AvLo condition ($x = -4$, $y = 16$, $z = 46$, Z score = 3.65) (Fig. 1, A to C). Regression analysis revealed positive linear correlation between self-rating scores of envy and the degree of activation in the dACC ($x = -2$, $y = 10$, $z = 52$, z score = 4.36) in SpHi-AvLo contrast (fig. S3, A and B). The MisSpHi-MisAvLo condition produced activations in the reward-related regions: the dorsal striatum (caudate, putamen) ($x = -16$, $y = -2$, $z = 16$, z score = 4.44), the ventral striatum including the nucleus accumbens ($x = -12$, $y = 6$, $z = -10$, z score = 4.41), and the medial orbitofrontal cortex ($x = -8$, $y = 54$, $z = -10$, z score = 3.46) (fig. S4, A and B). There was correlation between the intensity of schadenfreude and the degree of activation in the ventral striatum ($x = -14$, $y = 2$, $z = -12$, z score = 3.98) in MisSpHi-MisAvLo contrast (Fig. 2, A and B). dACC ($x = -2$, $y = 10$, $z = 52$) activation in SpHi-AvLo contrast was positively correlated with ventral striatum ($x = -14$, $y = 2$, $z = -12$) activation in MisSpHi-MisAvLo contrast (Fig. 3).

This study investigated the neurocognitive mechanisms of envy and schadenfreude and the role of social comparison in the central processing of these emotions. At the behavioral level in study one, the intensity of envy is modulated by the quality of the possession of the person we compare with and the self-relevance of the comparison domain. That is, if the possession of the target person is superior and the comparison domain is self-relevant, we feel intense envy.

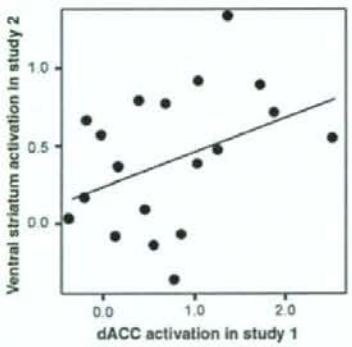

Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (–2, 10, 52). The y axis indicates the parameter estimates of the ventral striatum activation for MisSpHi-MisAvLo contrast at a peak voxel (–14, 2, –12). Positive correlation between dACC activation in study one and ventral striatum activation in study two across participants is shown ($r = 0.39$, $P = 0.01$).

When the comparison domain is not self-relevant, we do not feel strong envy, even if the possession is superior. When the comparison target is neither superior nor self-relevant, we are indifferent to the target. Activation of dACC was also modulated by possession quality and self-relevance. Stronger dACC activation was observed when one felt stronger envy. Moreover, between-participant correlation analysis demonstrated that people with stronger envy showed greater activation in dACC. At the behavioral level in study two, stronger schadenfreude was related to stronger envy, and schadenfreude arose when misfortune occurred to a person who was advantaged and self-relevant. Striatal activation was observed when misfortune happened to an envied person but not when it happened to a non-envied person. Between-participant analysis revealed that people with stronger schadenfreude showed greater activation in the ventral striatum.

ACC activation in response to envy stimuli might reflect a painful feature of this emotion. It was comparable to caudal ACC activation in response to pain in the self but not to pain in others (empathic pain) (*12*), suggesting that the participants experienced a painful feeling. Activation in this region has been reported in response to social pain (distress of social exclusion) (*20*). Taken together, envy might be a social pain in the self, with feelings of being excluded from the field that one is concerned with.

We are usually motivated to maintain a positive self-concept (*16*), and we feel discomfort when our self-concept is threatened by others who outperform ourselves in a self-relevant domain. Considering the role of dACC in conflict-monitoring (*19*), the association between envy and dACC activation suggests that envy is a condition in which information recognized by social comparison conflicts with positive self-concept. Experiencing discomfort motivates us to reduce it. Discomfort arising from others outperforming us in our cherished domains can be resolved by reducing the relevance of the domain to us or changing relative performance (*16*). Students in our scenario might change their major or club at the university and, ultimately, their goals in life. Alternatively, they might make an effort to improve their own performance or possession. On the contrary, they might wish that the other lacks advantages, or they may even obstruct the advantaged student (with malice). Similarly, from an economic perspective, envy has productive and destructive effects on economic growth. It motivates the members in organizations to enhance their own performances or to sabotage their opponents' performances (*24*). When misfortune occurs to an advantaged person and contributes to narrowing the gap of relative performance in an important domain, discomfort or pain is reduced, and a pleasant feeling is induced. This pleasure at another's misfortune is correspondent to the activation of the ventral striatum and the medial orbitofrontal cortex (*25*, *26*). The striatum has also been implicated in altruistic punishment (*27*) and observing an unfair person receiving pain (*28*). Stronger dACC activation induced by the most envied student in study one predicted stronger ventral striatum activation when misfortunes occurred to the student in study two. This means that people who tend to have higher pain or conflict are more likely to have a strong pleasant feeling once they are relieved from this pain. Thus, our findings propose a neurocognitive mechanism of a psychologically rewarding reaction, schadenfreude, and its relation to envy. At the same time, ventral striatum activation without receiving an actual reward indicates that we did not evaluate objects solely by their absolute value but that social comparison plays a substantial role in evaluation (*29*).

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30. We gratefully thank C. Frith for his valuable comments. This study was supported by a Health and Labor Sciences Research Grant for Comprehensive Research on Disability, Health, and Welfare (H20-SYOGAI-011) from the Japanese Ministry of Health, Labor, and Welfare, and a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H20-KOKORO-025) from the Japanese Ministry of Health, Labor, and Welfare. D.M. is support by MRC (UK).

Supporting Online Material

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8 September 2008; accepted 10 December 2008
10.1126/science.1165604

Schizophrenia Bulletin Advance Access published October 16, 2008

Schizophrenia Bulletin
doi:10.1093/schbul/sbn132

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 clumsiness[6] 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 al[18] 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 surrounding 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.

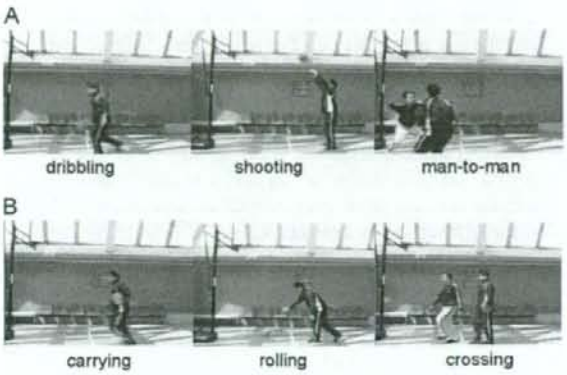

Fig. 1. Sample of Still Frames From Video Clips. A, Basketball-related motions; B, basketball-unrelated motions.

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

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	*t* value	voxels
		x	*y*	*z*			
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.

pallidus (table 1 and figure 2). The activations in a priori regions (EBA and STS) survived a threshold of $P < .05$ 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.

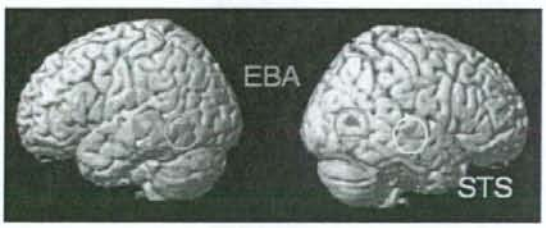

Fig. 2. Images Showing the Brain Area of Diminished Activations in Response to Basketball-Related Motions (BRM) Relative to Basketball-Unrelated Motions (BUM) Condition in 12 Patients With Schizophrenia Compared With 12 Normal Controls. Diminished activations in the bilateral extrastriate body area (EBA), 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 al[29]). 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 studies have suggested that the EBA is also directly involved in representing the dynamic aspects of human

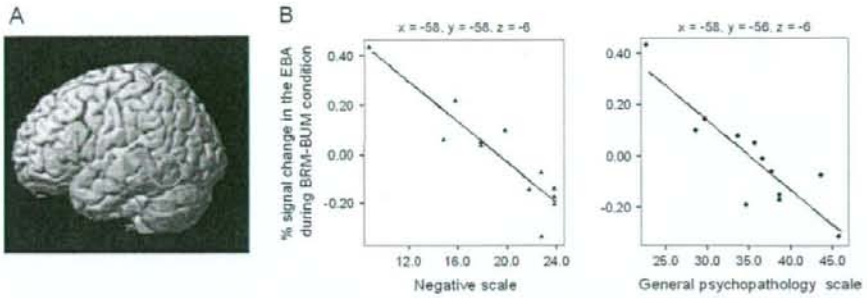

Fig. 3. Negative Correlations Between Positive and Negative Syndrome Scale (PANSS) Scores and the Degree of Activation in the Extrastriate Body area (EBA). A, Images showing negative correlation between negative scale scores and the degree of activation in the left EBA in basketball-related motions-basketball-unrelated 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 ($r = -0.88$, $df = 10$; $P < .001$).

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.

Funding

Japanese Ministry of Health, Labor and Welfare (Health and Labor Sciences Research Grant for Research on

Psychiatric and Neurological Diseases and Mental Health H20-KOKORO-025).

Acknowledgments

Mieko Mori and Harumi Murayama and the staff of the day hospital unit of Asai Hospital are gratefully acknowledged for nursing care and assistance with subject recruitment.

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Behavioral/Systems/Cognitive

Differential Contributions of Prefrontal and Hippocampal Dopamine D_1 and D_2 Receptors in Human Cognitive Functions

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Dopamine D_1 receptors in the prefrontal cortex (PFC) are important for prefrontal functions, and it is suggested that stimulation of prefrontal D_1 receptors induces an inverted U-shaped response, such that too little or too much D_1 receptor stimulation impairs prefrontal functions. Less is known of the role of D_2 receptors in cognition, but previous studies showed that D_2 receptors in the hippocampus (HPC) might play some roles via HPC–PFC interactions. We measured both D_1 and D_2 receptors in PFC and HPC using positron emission tomography in healthy subjects, with the aim of elucidating how regional D_1 and D_2 receptors are differentially involved in frontal lobe functions and memory. We found an inverted U-shaped relation between prefrontal D_1 receptor binding and Wisconsin Card Sorting Test performance. However, prefrontal D_2 binding has no relation with any neuropsychological measures. Hippocampal D_2 receptor binding showed positive linear correlations not only with memory function but also with frontal lobe functions, but hippocampal D_1 receptor binding had no association with any memory and prefrontal functions. Hippocampal D_2 receptors seem to contribute to local hippocampal functions (long-term memory) and to modulation of brain functions outside HPC ("frontal lobe functions"), which are mainly subserved by PFC, via the HPC–PFC pathway. Our findings suggest that orchestration of prefrontal D_1 receptors and hippocampal D_2 receptors might be necessary for human executive function including working memory.

Key words: dopamine; D_1 receptors; D_2 receptors; prefrontal cortex; hippocampus; positron emission tomography

Introduction

Because dopamine D_1 receptors in the prefrontal cortex (PFC) are several times more abundant than D_2 receptors (Hall et al., 1994), the relationship between D_1 receptors and PFC functions have been widely investigated. Sawaguchi and Goldman-Rakic (1994) demonstrated that local administration of D_1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate. In human, Müller et al. (1998) reported that systemic administration of a mixed D_1/D_2 agonist facilitated working memory, whereas the selective D_2 agonist had no effect, indicating that the dopaminergic modulation of working memory processes is mediated primarily via D_1 receptors. The use of positron emission tomography (PET) allows us to quantify dopamine receptors *in vivo*, and previous studies reported that altered prefrontal D_1 receptors in schizophrenia were associated with working memory deficits (Okubo et al., 1997; Abi-Dargham et al., 2002).

In contrast to D_1 receptors, relatively less attention has been paid to the role of prefrontal D_2 receptors in cognitive functions. It was reported that blockade of D_2 receptors in PFC did not impair working memory in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994), but some human studies reported that systemic administration of D_2 agonist or antagonist modulated cognitive functions that are subserved by the prefrontal cortex (McDowell et al., 1998; Mehta et al., 1999). Because the density of D_2 receptors in extrastriatal regions is very low (Suhara et al., 1999), PET studies investigating the involvement of extrastriatal D_2 receptors in cognition have been limited. With the introduction of high-affinity PET radioligands such as [^{11}C]FLB457, it has become possible to quantify extrastriatal D_2 receptors by PET (Halldin et al., 1995). Using [^{11}C]FLB457, Kemppainen et al. (2003) reported that a reduction of D_2 receptors in the hippocampus (HPC) in Alzheimer's disease patients was correlated with memory impairments. Our recent PET study also showed that D_2 receptors in HPC were associated not only with memory function but also with frontal lobe functions (Takahashi et al., 2007), suggesting dopaminergic modulation on HPC–PFC inter-

Received July 23, 2008; revised Sept. 2, 2008; accepted Oct. 2, 2008.

This work was supported by a consignment expense for Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), the Japanese Government, and a Grant-in-Aid for Scientific Research from MEXT (18790858). We thank Katsuyuki Tanimoto, Takahiro Shiraishi, and Toshio Miyamoto for their assistance in performing the PET experiments at the National Institute of Radiological Sciences. We also thank Yoshiko Fukushima of the National Institute of Radiological Sciences for her help as clinical research coordinator.

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DOI:10.1523/JNEUROSCI.3446-08.2008

 0270-6474/08/2812032-07$15.00/0

actions during the cognitive process (Laroche et al., 2000; Thierry et al., 2000; Goto and Grace, 2008).

In this study, we measured both D_1 and D_2 receptors in PFC and HPC using PET in normal healthy subjects, and aimed to elucidate how regional D_1 and D_2 receptors are differentially involved in neurocognitive performance including memory and frontal lobe functions. A body of animal studies has indicated that stimulation of D_1 receptors in PFC produces an inverted U-shaped dose–response curve, such that too little or too much D_1 receptor stimulation impairs PFC functions (Goldman-Rakic et al., 2000; Williams and Castner, 2006; Vijayraghavan et al., 2007). We hypothesized that prefrontal D_1 receptors would be more related to frontal lobe functions than prefrontal D_2 receptors, and that, specifically, an inverted U-shaped relation between prefrontal D_1 receptor binding and prefrontal functions would be observed in the normal physiological condition in healthy volunteers. In addition, we predicted that D_2 receptors in HPC would be more related to memory than D_1 receptors in HPC.

Materials and Methods

Subjects. Twenty-three healthy male volunteers [mean age 25.7 ± (SD) 4.3 years] were studied. Seven of the 23 subjects had participated in our earlier study (Takahashi et al., 2007). They did not meet the criteria for any psychiatric disorder based on unstructured psychiatric screening interviews. None of the controls were using 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 magnetic resonance imaging (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.

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. For evaluation of D_1 receptors, a bolus of 213.9 ± 20.5 MBq of [^{11}C]SCH23390 with specific radioactivities (52.1 ± 28.9 GBq/μmol) was injected intravenously from the antecubital vein with a 20 ml saline flush. For evaluation of extrastriatal D_2 receptors, a bolus of 215.4 ± 24.5 MBq of [^{11}C]FLB457 with high specific radioactivities (171.0 ± 58.0 GBq/μmol) was injected in the same way. The mean injected amounts of [^{11}C]SCH23390 and [^{11}C]FLB457 were 1.18 ± 0.20 μg and 0.47 ± 0.17 μg, respectively. Dynamic scans were performed for 60 min for [^{11}C]SCH23390 and 90 min for [^{11}C]FLB 457 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. The scan parameters were 1-mm-thick, three-dimensional T1 images with a transverse plane (repetition time/echo time, 19/10 milliseconds; 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 in PFC and HPC. The tissue concentrations of the radioactivities of [^{11}C]SCH23390 and [^{11}C]FLB457 were obtained from regions of interest (ROIs) defined on the PET images of summated activity for 60 and 90 min, respectively, with reference to the individual MRIs that were coregistered on summated PET images and the brain atlas. The regions were PFC, HPC and cerebellar cortex. Each ROI consisted of three axial slices. ROI of PFC occupies the middle third of the middle frontal gyrus and the rostral portion of the inferior frontal gyrus (approximately corresponding to the dorsolateral prefrontal cortex or Brodmann area 46). ROI of HPC was set at the level of the midbrain. The anterior boundary was identified at the level of the inferior horn of the lateral ventricle. The posterior boundary was identified at the level of the collateral sulcus. 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 (Olsson et al., 1999; Suhara et al., 1999). Quantitative analysis was performed using the three-parameter simplified reference tissue model (Lammertsma and Hume, 1996). The cerebellum was used as reference region because it has been shown to be almost devoid of D_1 and D_2 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: $BP_{ND} = k3/k4 = f2\ Bmax/[Kd\ [1 + \sum i\ Fi/Kdi]]$, where k3 and k4 describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, f2 is the "free fraction" of nonspecifically bound radioligand in brain, Bmax is the receptor density, Kd is the equilibrium dissociation constant for the radioligand, and Fi and Kdi are the free concentration and the dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996).

Neuropsychological tests. A battery of cognitive tests was given by an experienced clinical neuropsychologist. The neuropsychological tests used were Rey's Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth's Complex Figure Test (ROCFT), Keio version of the Wisconsin Card Sorting Test (WCST) (Igarashi et al., 2002), Verbal Fluency Test, and Raven's Colored Progressive Matrices (RCPM). RAVLT is used to evaluate the performance of verbal memory, and ROCFT is used as a measure of nonverbal visual memory. RAVLT and ROCFT were performed in the standard manner (Lezak, 1995). In RAVLT, 15 words were presented auditorily in the same sequence in five trials, ending with a free recall of the words (immediate recall). After the five trials, an interference list was presented and recalled, and then the subjects were instructed to recall the first list of words (delayed recall). In ROCFT, after the copy trial, subjects were asked to reproduce a figure from memory (immediate recall). After a 15 min pause, the subjects were asked to reproduce the figure from memory again (delayed recall). WCST is a test for executive function or cognitive flexibility involving working memory (Berman et al., 1995). It has been shown to be sensitive to dysfunction of PFC (Nelson, 1976). In WCST, categories achieved (CA), total errors (TE) and perseverative errors of Nelson (PE) were evaluated (Lezak, 1995). In the phonemic verbal fluency test, the subject was requested to retrieve in 1 min as many words as possible beginning with the Japanese syllabic characters (hiragana) "shi," "i" and "re," respectively. In the semantic verbal fluency test, the subject was requested to recall in 1 min as many words as possible belonging to a given semantic category (e.g., animals, fruit) (Lezak, 1995). RCPM was used as a general visuospatial intelligence test.

Statistical analyses. Although the selection of subjects was confined to young males in their 20's and 30's, the possible age effect on the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457, and neuropsychological performance were examined using Pearson correlation analysis. To explore the relation between D_1 and D_2 receptors and cognitive functions, linear regression between the BP_{ND} values of each ROI and each neuropsychological performance was analyzed, and the threshold for significance was set at $p = 0.05/2 = 0.025$ to correct for two regions (PFC and HPC). Although a single dominant factor underlying the scores on all tests, i.e., general cognitive ability, might contribute to intercorrelations across the tests, what we measure with neuropsychological tests is, by nature, a dimensionality of cognitive ability. Therefore, correction of p values for multiple comparisons was done only for regions, not for multiple neuropsychological tests. To examine putative nonlinear (inverted U-shaped) relations between prefrontal dopamine receptors and frontal lobe functions, quadratic regression between the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and neuropsychological performance was analyzed by SPSS package (SPSS).

To confirm the findings of the ROI analysis, parametric images of BP_{ND} (Gunn et al., 1997) were analyzed using statistical parametric mapping software (SPM2) (Wellcome Department of Imaging, Institute of Neurology, University College of London, London, UK). Normalized BP_{ND} images were smoothed with a Gaussian filter to 16 mm full-width

Table 1. Mean scores of neuropsychological tests and linear relations between and neuropsychological measures and BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in the prefrontal cortex and hippocampus

Neuropsychological tests	Mean scores	Prefrontal cortex r (p)		Hippocampus r (p)	
		[^{11}C]SCH23390	[^{11}C]FLB457	[^{11}C]SCH23390	[^{11}C]FLB457
RALVT immediate	57.3 ± 6.2	0.07 (0.74)	0.16 (0.47)	0.10 (0.66)	0.37 (0.09)
RALVT delayed	13.0 ± 1.5	0.14 (0.53)	0.02 (0.94)	0.08 (0.72)	0.28 (0.20)
ROCFT immediate	27.7 ± 3.9	0.11 (0.63)	0.31 (0.15)	0.21 (0.34)	0.73 (p<0.001)**
ROCFT delayed	27.3 ± 4.8	0.12 (0.58)	0.38 (0.07)	0.11 (0.60)	0.67 (p<0.001)**
WCST CA	5.4 ± 1.2	0.42 (0.049)*	0.03 (0.89)	0.21 (0.33)	0.30 (0.17)
WCST TE	11.3 ± 3.7	−0.41 (0.049)*	−0.15 (0.51)	−0.30 (0.16)	−0.51 (0.01)**
WCST PE	0.8 ± 1.4	−0.27 (0.21)	−0.18 (0.42)	−0.31 (0.15)	−0.59 (0.003)**
Phonemic verbal fluency	30.9 ± 9.3	0.21 (0.35)	0.21 (0.34)	0.20 (0.36)	0.47 (0.02)**
Semantic verbal fluency	46.1 ± 7.9	−0.07 (0.76)	0.09 (0.69)	0.06 (0.77)	0.17 (0.45)
RCPM (sec)	188.5 ± 36.0	0.10 (0.65)	−0.04 (0.87)	0.11 (0.64)	0.08 (0.70)

*p < 0.05. **Significant after correction for multiple statistical tests (new significance threshold: p < 0.025[0.05/2]).

half-maximum. Using each individual cognitive performance as covariate, regression analyses with the BP_{ND} images and the covariates were performed.

Results

The mean [^{11}C]SCH23390 BP_{ND} values of PFC and HPC were 0.41 ± 0.06 (range: 0.29–0.59) and 0.33 ± 0.09 (range: 0.20–0.53), respectively. The mean [^{11}C]FLB457 BP_{ND} values of PFC and HPC were 1.16 ± 0.21 (range: 0.82–1.58) and 1.57 ± 0.28 (range: 0.98–1.92), respectively. The mean scores of the neuropsychological data are shown in Table 1. There was no age effect on the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in the two ROIs, nor on any neuropsychological performance ($p > 0.01$).

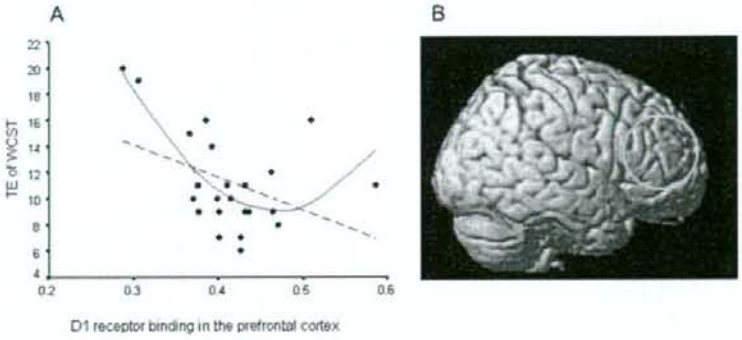

Figure 1. Quadratic (inverted U-shaped) relation between D_1 receptor binding in PFC and performance of WCST. ***A***, ROI analysis revealed a significant quadratic regression between the BP_{ND} value of [^{11}C]SCH23390 in PFC ($BP_{D1\,PFC}$) and TE of WCST. Red solid line, quadratic regression; black broken line, linear regression. Based on ROI analysis, the relation between $BP_{D1\,PFC}$ and TE can be expressed as follows: $TE = 326.92(BP_{D1\,PFC} - 0.47)^2 + 9.10$. ***B***, Using this equation, SPM analysis also revealed a significant quadratic regression between prefrontal D_1 receptor binding and TE of WCST ($p < 0.001$, uncorrected, extent threshold >30 voxels).

Quadratic regression analysis revealed a significant "U-shaped" relation between the BP_{ND} value of [^{11}C]SCH23390 in PFC and TE of WCST ($p < 0.001$, $r = 0.72$). (Because TE of WCST is a negative measure of frontal lobe function, the relation is not "inverted") (Fig. 1). The BP_{ND} value of [^{11}C]SCH23390 in PFC and CA of WCST also showed significant quadratic (inverted U-shaped) relation ($p < 0.001$, $r = 0.78$). However, no quadratic relation was found between the BP_{ND} value of [^{11}C]FLB 457 in PFC and any neuropsychological measures. The linear relations between neuropsychological measures and the BP_{ND} value of each ROI are shown in Table 1. As for D_1 receptors, the BP_{ND} value of [^{11}C]SCH23390 in PFC was positively correlated with CA of WCST ($p = 0.049$, $r = 0.42$), and negatively correlated with TE of WCST ($p = 0.049$, $r = -0.41$) although these relations did not survive a threshold corrected for multiple comparisons. The BP_{ND} value of [^{11}C]SCH23390 in HPC was not correlated with any neuropsychological measures. With regard to D_2 receptors, the BP_{ND} value of [^{11}C]FLB457 in HPC was positively correlated with immediate and delayed recall scores of ROCFT and phonemic verbal fluency, and negatively correlated with CA and TE of WCST. The BP_{ND} value of [^{11}C]FLB457 in PFC was not correlated with any neuropsychological measures. Figure 2 shows these relationships.

D_1 binding in PFC showed significant correlation with D_1 binding in HPC ($r = 0.74$, $p < 0.001$) and trend level correlation with D_2 binding in PFC ($r = 0.41$, $p = 0.05$), but no correlation with D_2 binding in HPC ($r = 0.27$, $p = 0.22$). D_2 binding in HPC showed significant correlation with D_2 binding in PFC ($r = 0.50$, $p = 0.02$) and trend level correlation with D_1 binding in HPC ($r = 0.36$, $p = 0.09$). D_2 binding in PFC showed no correlation with D_1 binding in HPC.

Using SPM2, we conduced standard voxel-based morphometry without modulation (Ashburner and Friston, 2000) to test whether the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and HPC were related to the prefrontal and hippocampal gray matter concentration in the normalized images, respectively. The age and total gray matter (GM) volume were treated as confounding covariates in an analysis of covariance. The total GM volume was given by the total number of voxels within the GM compartment of each subject. The analysis revealed that there were no significant correlations between the BP values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and HPC and the concentration of gray matter in the prefrontal and hippocampal regions, respectively, at a threshold of $p = 0.01$, uncorrected.

Discussion

Although D_1 receptor binding in PFC showed trend-level positive linear correlations with WCST performance, quadratic regression analysis revealed significant inverted U-shaped relations between D_1 receptors in PFC and WCST performance. That is, a too high or too low level of D_1 receptor expression in PFC leads to high errors and a low number of categories achieved. However, D_2 receptor binding in PFC did not show significant relation with

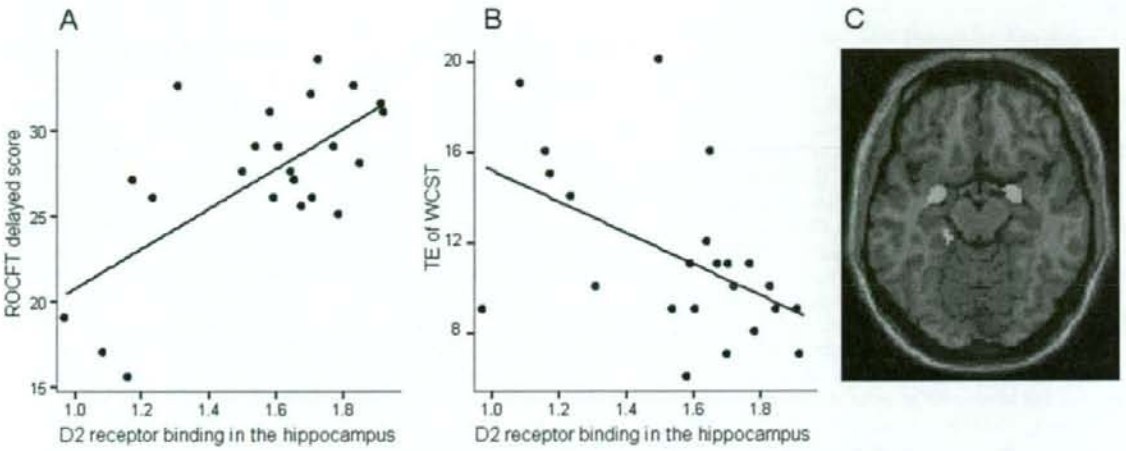

Figure 2. Correlations between D_2 receptor binding in the hippocampus and memory. ***A***, ***B***, Significant positive linear correlations between the BP_{ND} value of [^{11}C]FLB457 in the hippocampus and the delayed recall score of ROCFT and (***B***) TE of WCST revealed by ROI analysis. ***C***, The SPM result of a positive linear correlation between hippocampal D_2 receptor binding and the delayed recall score of ROCFT is shown ($p < 0.005$, uncorrected, extent threshold >30 voxels).

any neuropsychological measures. With regard to dopamine receptors in HPC, D_2 receptor binding in HPC showed positive liner correlations not only with memory function but also with frontal lobe functions, whereas D_1 receptor binding in HPC did not show significant relation with any neuropsychological measures. WCST involves a set-shifting component as well as a working memory component, although the two abilities are not mutually exclusive (Konishi et al., 1999). Working memory requires the active maintenance and manipulation of trial-unique information in a short-term memory buffer (Goldman-Rakic, 1995; Fuster, 2000). Thus, set-shifting could be regarded as updating of working memory content, and it has been demonstrated that updating of working memory content and shifting of cognitive set have a similar cognitive aspect in common (Konishi et al., 1998). Thus, in normal human subjects, the individual difference of working memory capacity could contribute to the difference in the performance of tests for cognitive flexibility.

Previous animal studies demonstrated that local injection of D_1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994). In a human study, systemic administration of a mixed D_1/D_2 agonist, pergolide, facilitated working memory, but the selective D_2 agonist bromocriptine had no effect, indicating that the dopaminergic modulation of working memory is mediated primarily via stimulation of D_1 receptors (Müller et al., 1998). Subsequent animal studies indicated that stimulation of D_1 receptors in PFC produces an inverted U-shaped response in working memory, with the response being optimized within a narrow range of D_1 receptor stimulation (Goldman-Rakic et al., 2000; Lidow et al., 2003; Castner and Goldman-Rakic, 2004; Seamans and Yang, 2004; Vijayraghavan et al., 2007). Recent human studies have investigated the effect of a functional polymorphism in the catechol *O*-methyltransferase gene, which has been shown to modulate the prefrontal dopamine level, on prefrontal function. The results also suggested that dopamine transmission in PFC produces an inverted U-shaped response, meaning that too little or too much dopamine signaling would impair prefrontal functions, although these studies could not identify the receptor subtype that plays a central role in this effect (Mattay et al., 2003; Williams-Gray et al., 2007).

Our PET finding is the first direct evidence in human that demonstrated an inverted U-shaped relation between D_1 receptors in PFC and executive function including working memory in normal healthy subjects. Our previous PET study revealed that, compared with normal controls, D_1 receptors in PFC were decreased in schizophrenia, which was associated with poor performance on WCST (Okubo et al., 1997). However, another PET study reported that an increase in D_1 receptors in PFC was associated with working memory deficits in schizophrenia (Abi-Dargham et al., 2002). It has been discussed that these inconsistent results might stem from several factors including differences in radioligands and patient demographics. Although the reasons for these inconsistent results need to be clarified in the future, an inverted U-shaped response can account for working memory deficits in schizophrenia whether D_1 receptors in PFC are increased or decreased in patients, because the D_1 receptor inverted U-shaped response is observed within a narrow range of the normal physiological condition (Williams and Castner, 2006; Vijayraghavan et al., 2007). An inverted U-shaped response has been suggested based on cognitive and behavioral studies, but the exact physiological mechanism of this effect has not yet been fully understood. A recent monkey electrophysiology study has demonstrated a neuron-level mechanism that constitutes the inverted U-shaped response whereby too much or too little stimulation of prefrontal D_1 receptors leads to working memory deficits. D_1 receptor stimulation had a suppressive effect on the PFC neural activities involved in a spatial working memory task. Moderate D_1 receptor stimulation spatially tunes PFC neurons that process target signals by preferentially suppressing nontarget (noisy) neural activities, whereas excessive D_1 receptor stimulation induces nonselective suppression of PFC neural activities regardless of whether the neural activities are task-related or not (Vijayraghavan et al., 2007).

Animal studies have suggested that the inverted U-shaped principle of D_1 receptor stimulation mediating working memory does not necessarily apply to other prefrontal functions (Floresco and Magyar, 2006). Therefore, it is noteworthy that prefrontal D_1 receptors were not associated with other prefrontal measures besides WCST, because fluency task by phonetic or semantic cues

and problem-solving test with visuospatial analysis are less dependent on the working memory process.

Considering that D_1 binding in PFC was not correlated significantly with D_2 binding either in PFC or HPC, D_1- and D_2-mediated working memory processes are considered to contribute differently to the completion of WCST. Although previous animal studies showed that working memory or executive function mainly depends on D_1 receptors, not on D_2 receptors in PFC (Sawaguchi and Goldman-Rakic, 1994; Seamans et al., 1998), a recent rat study demonstrated that D_2 receptors in PFC were necessary for set-shifting ability (Floresco et al., 2006). It has been suggested that when the dopamine level is high under a novel circumstance, the prefrontal network is mainly modulated by D_2 receptors. In such state, the network is likely to process multiple information (Seamans and Yang, 2004; Floresco et al., 2006). During the set-shifting stage of WCST, one needs to disengage from the previous strategy and compare alternative options under a new condition. After shifting attentional sets, one needs to learn and maintain a new strategy of WCST. In such condition, the dopamine level is considered to be moderate and D_1 receptors play a central role in stabilizing the network (Seamans and Yang, 2004; Floresco et al., 2006). We did not find any correlation between D_2 binding in PFC and WCST performances, possibly attributable to the fact that the working memory component and the set-shifting component are not entirely dissociable in WCST (Konishi et al., 1999). Instead, D_2 binding in HPC was related to WCST performances. Although the role of hippocampal D_2 receptors in set-shifting is not known, a possible interpretation is that in the initial set-shifting stage of WCST, D_2 receptors in HPC might play a role in quick learning and comparison to guide future behaviors, and once a new strategy is learned, D_1 receptors in PFC might contribute to the stability and maintenance of the novel strategy.

The association between hippocampal D_2 receptors and memory is consistent with the findings of previous PET studies (Kemppainen et al., 2003; Takahashi et al., 2007). The finding that hippocampal D_2 binding was more related to visuospatial memory than to verbal memory might stem from the fact that verbal learning is dependent on regions other than HPC, such as anterior, lateral and superior temporal lobes, which are involved in human language, although HPC plays a central role in both types of memory (Hodges and Graham, 2001). Umegaki et al. (2001) reported that injection of a D_2 receptor antagonist into HPC impaired memory performance and that the memory impairment was ameliorated by coinjection of a D_2 receptor agonist. They also found that local infusion of D_2 agonist into HPC stimulated acetylcholine release in HPC and ameliorated scopolamine-induced memory impairment (Fujishiro et al., 2005). In addition, hippocampal D_2 receptors appear to be involved in synaptic plasticity. It has been reported that D_2 antagonist inhibited long-term potentiation in HPC (Frey et al., 1990; Manahan-Vaughan and Kulla, 2003), the key mechanism underlying memory consolidation (Jay, 2003; Lynch, 2004). There is some evidence from animal studies that hippocampal D_1 receptors are also involved in memory (Hersi et al., 1995a,b; Bach et al., 1999), but supporting our PET data, Wilkerson and Levin (1999) reported that hippocampal D_1 receptors were not as responsible as D_2 receptors for memory functions.

In line with our previous study (Takahashi et al., 2007), we also found hippocampal D_2 receptors to be involved in the performance of WCST and phonemic verbal fluency, which is more dependent on PFC than semantic verbal fluency. Patients with lesions in HPC sometimes show deficits in WCST (Corkin, 2001; Igarashi et al., 2002). These observations suggest that hippocampal D_2 receptors could modulate PFC activity by the HPC–PFC pathway, which plays a significant role in the cognitive process (Laroche et al., 2000; Thierry et al., 2000). Accumulating evidence has suggested the modulatory effects of dopamine on HPC–PFC interactions (Seamans et al., 1998; Aalto et al., 2005; Tseng et al., 2007; Goto and Grace, 2008). Conceivably, dopamine influences PFC neurons directly by prefrontal D_1 receptors and indirectly by hippocampal D_2 receptors via the HPC–PFC pathway.

Müller et al. (1998) reported that the systemic administration of the mixed D_1/D_2 agonist pergolide facilitated working memory, whereas selective D_2 agonist had no effect. However, there is converging evidence from human and animal studies to suggest the involvement of D_2 receptors in cognitive functions. It was reported that the systemic administration of D_2 agonist in human improved cognitive functions including working memory and executive functions (McDowell et al., 1998), and the administration of D_2 antagonist impaired those functions (Mehta et al., 1999). In an animal study, it was reported that mice lacking D_2 receptors showed a working memory deficit (Glickstein et al., 2002). These studies, however, did not reveal the regions most responsible for these effects. Moreover, although the involvement of D_1 receptors in working memory is widely recognized, it was not clear whether D_1 receptor stimulation alone or the combination of D_1 and D_2 receptor stimulation is most effective. Our finding suggested that orchestration of prefrontal D_1 receptors and hippocampal D_2 receptors might be necessary for executive functions including working memory.

The current study has several limitations. First, although BP_{ND} is the complex value of receptor density and affinity (the inverse of Kd), previous studies indicated that the affinity does not differ according to region (Suhara et al., 1999) and that extrastriatal binding of current PET ligands is not sensitive to endogenous dopamine (Abi-Dargham et al., 1999; Okauchi et al., 2001). Still, we should keep in mind that the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 might not necessarily be equivalents for D_1 and D_2 receptor functions, respectively. This emphasizes the need for PET investigations of the relation of BP_{ND} and presynaptic function or second messenger beyond dopamine receptors. Alternatively, multimodal imaging study combining the current method with other modalities such as functional MRI might also be advantageous in investigating the direct relation between dopamine receptor function and PFC functions. Second, we measured the level of dopamine receptor binding during a resting state rather than during cognitive tasks. It is difficult to measure endogenous dopamine release in extrastriatal regions with the current PET ligands (Abi-Dargham et al., 1999; Okauchi et al., 2001). Future study with radioligands more sensitive to endogenous dopamine release will enable us to examine its degree of receptor occupancy. Finally, attributable to limitations of the [^{11}C] radioligand, the data of [^{11}C] FLB457 binding in the striatum was not available. The striatum plays an important role in the prefrontal-hippocampus pathway. PET data in the striatum would lead to a better understanding of the interaction of these three regions. Future study with triple radioligands such as [^{11}C]SCH23390, [^{11}C] FLB457 and [^{11}C] raclopride will enable us to examine striatal and extrastriatal D_1 and D_2 receptors in the same subject.

In summary, we found that an inverted U-shaped relation existed between D_1 receptor binding in PFC and WCST performance, indicating an inverted U-shaped relation between prefrontal D_1 receptors and working memory, and that prefrontal D_2 receptor binding was not related to any frontal lobe functions.

Hippocampal D_2 receptors seem to contribute to local hippocampal functions (long-term memory) and to modulation of brain functions outside HPC (frontal lobe functions), which are mainly subserved by PFC, via the HPC–PFC pathway. Our findings suggest that prefrontal D_1 receptors and hippocampal D_2 receptors might be targets for pharmacological therapeutics for cognitive and memory impairments observed in neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease and schizophrenia.

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