Enomoto M, Tsutsui T, Higashino S, Otaga M, Higuchi S, Aritake S, Hida A, Tamura M, Matsuura M, Kaneita Y, Takahashi K, Mishima K	Sleep-related problems and use of hypnotics in inpatients of acute hospital wards	Gen Hosp Psychiatry	32	276-283	2010
Aritake-Okada S, Uchiyama M, Suzuki H, Tagaya H, Kuriyama K, Matsuura M, Takahashi K, Higuchi S, Mishima K	Time estimation during sleep relates to the amount of slow wave sleep in humans	Neurosci Res	63	115–121	2009
Enomoto M, Endo T, Suenaga K, Miura N, Nakano Y, Kohtoh S, Taguchi Y, Aritake S, Higuchi S, Matsuura M, Takahashi K, Mishima K	Newly developed waist actigraphy and its sleep/wake scoring algorithm	Sleep Biol Rhythms	7	17-22	2009
Fukumoto-Motoshita M, Matsuura M, Ohkubo T, Ohkubo H, Kanaka N, Matsushima E, Taira M, Kojima T, Matsuda T	Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: a study with fMRI	Psychiatry Clin Neurosci	63	209-217	2009
Hirota S, Matsuura M, Masuda H, Ushiyama A, Wake K, Watanabe S, Taki M, Ohkubo C	Direct observation of microcirculatory parameters in rat brain after local exposure to radio-frequency electromagnetic field	Environmenta list	29	186-189	2009
Kamei S, Morita A, Tanaka N, Matsuura M, Moriyama M, Kojima T, Arakawa Y, Matsukawa Y, Mizutani T, Sakai T, Oga K, Ohkubo H, Matsumura H, Hirayanagi K	Relationships between quantitative electroencephalographic alterations and the severity of hepatitis C based on liver biopsy in interferon-α treated patients	Inter Med	48	975-980	2009
Suzuki M, Takahashi S, Matsushima E, Tsunoda M, Kurachi M, Okada T, Hayashi T, Ishii Y, Morita K, Maeda H, Katayama S, Kawahara R, Otsuka T, Hirayasu Y, Sekine M, Okubo Y, Motoshita M, Ohta K, Uchiyama M, Kojima T:	Exploratory eye movement dysfunction as a discriminator for schizophrenia : a large sample study using a newly developed digital computerized system.	*Eur Arch Psychiatry Clin Neurosci*	259	186-194	2009
Otsuka T., Ito H., Halldin C., Takahashi H., Takano H., Arakawa R., Okumura M., Kodaka F., Miyoshi M., Sekine M., Seki C., Nakao R., Suzuki K., Finnema S., Hirayasu Y., Suhara T., Farde L	Quantitative PET-analysis of the dopamine D2 receptor agonist radioligand [11C]MNPA in human brain.	*J Nucl Med*	50	703-710	2009
Ito H, Arakawa R, Takahashi H, Takano	No regional difference in dopamine D2	*Int J*	12	667-675	2009

H, Okumura M, Otsuka T, Ikoma Y, Shidahara M, Suhara T	receptor occupancy by secondgeneration antipsychotic drug risperidone in humans: a positron emission tomography study.	*Neuropsychopharmacol*			
Ito H, Takano H, Takahashi H, Arakawa R, Miyoshi M, Kodaka F, Okumura M, Otsuka T, Suhara T	Effects of the antipsychotic risperidone on dopamine synthesis in human brain measured by positron emission tomography with L-[11C]DOPA: a stabilizing effect for dopaminergic neurotransmission?	*J Neurosci*	29	13730-13734	2009
Arakawa R, Ito H, Okumura M, Morimoto T, Seki C, Takahashi H, Takano A, Suhara T	No inhibitory effect on P-glycoprotein function at blood-brain barrier by clinical dose of clarithromycin: a human PET study with [11C]verapamil	*Ann Nucl Med*			In press
Shidahara M, Ito H, Otsuka T, Ikoma Y, Arakawa R, Kodaka F, Seki C, Takano H, Takahashi H, Turkheimer FE, Kimura Y, Kanno I, Suhara T	Measurement error analysis for the determination of dopamine D(2) receptor occupancy using the agonist radioligand [(11)C]MNPA.	*J Cereb Blood Flow Metab*			In press
Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, Ito H, Okubo Y:Electroconvulsive therapy decreases dopamine D(2) receptor binding in the anterior cingulate in patients with depression: a controlled study using positron emission tomography with radioligand [(11)C]FLB 457.	Electroconvulsive therapy decreases dopamine D(2) receptor binding in the anterior cingulate in patients with depression: a controlled study using positron emission tomography with radioligand [(11)C]FLB 457.	*J Clin Psychiatry,*			In press
Nozaki S, Kato M, Takano H, Ito H, Takahashi H, Arakawa R, Okumura M, Fujimura Y, Matsumoto R, Ota M, Takano A, Otsuka A, Yasuno F, Okubo Y, Kashima H, Suhara T	Regional dopamine synthesis in patients with schizophrenia using L-[beta-11C]DOPA PET.	*Schizophr Res*	108	78-84	2009
Hirayasu Y, Kawanishi C, Yonemoto N, Ishizuka N, Okubo Y, Sakai A, Kishimoto T, Miyaoka H, Otsuka K, Kamijo Y, Matsuoka Y, Aruga T	A randomized controlled multicenter trial of post-suicide attempt case management for the prevention of further attempts in Japan (ACTION-J).	*BMC Public Health*	9	364	2009
Tateno M, Sugiura K, Uehara K, Fujisawa D, Zhao Y, Hashimoto N,	Attitude of young psychiatrists toward coercive measures in psychiatry: a case	*Int J Ment Health Syst.*	3	20	2009

Takahashi H, Yoshida N, Kato T, Nakano W, Wake Y, Shirasaka T, Kobayashi S, Sato S.	vignette study in Japan.				
Arakawa R, Ito H, Okumura M, Takano A, Takahashi H, Takano H, Okubo Y, Suhara T	Extrastriatal dopamine D(2) receptor occupancy in olanzapine-treated patients with schizophrenia.	*Eur Arch Psychiatry Clin Neurosci,*			In press
Arakawa R, Ichimiya T, Ito H, Takano A, Okumura M, Takahashi H, Takano H, Yasuno F, Kato M, Okubo Y, Suhara T	Increase in thalamic binding of [(11)C]PE2I in patients with schizophrenia: a positron emission tomography study of dopamine transporter.	*J Psychiatr Res*	43	1219-1223	2009
Tatsuhiko Yagihashi, Motoichiro Kato, Kosuke Izumi, Rika Kosaki, Kaori Yago, Kazuo Tsubota, Yuji Sato, Minoru Okubo, Goro Watanabe, Takao Takahashil, Kenjiro Kosaki	Case Report: Adult Phenotype of Mulvihill-Smith Syndrome	*American Journal of Medical Genetics*	Part A 149A	496-500	2009
Akira Uno, Taeko N. Wydell, Motoichiro Kato, Kanae Itoh, Fumihiro Yoshino	Cognitive Neuropsychological and Regional Cerebral Blood Flow Study of a Japanese-English Bilingual Girl with Specific Language Impairment (SLI)	*Cortex*	45	154-163	2009
Ando,N.,Iwamitsu,Y.,Takemura,K.,Saito,Y. Takada,F.	Impressions regarding the concept of mutation among family members of patients receiving outpatient genetic services	*Journal of Genetic Counseling*	18	567–577	2009
佐藤菜生,高崎いゆき,吉川肇子,村尾智,竹村和久	鉱物資源乱掘に従事する労働者のリスク認知—描画法を用いた事例研究—	リスク研究学会誌	19	33-41	2009
竹村和久	消費者の意思決定過程	基礎心理学研究	28	147-155	2009
竹村和久	意思決定と神経経済学	臨床精神医学	38	35-42	2009

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.

References and Notes

1. T. Hayashi, T. P. Su, *CNS Drugs* **18**, 269 (2004).
2. P. Bouchard *et al.*, *Eur. J. Neurosci.* **7**, 1952 (1995).
3. T. P. Su, A. D. Weissman, S. Y. Yeh, *Life Sci.* **38**, 2199 (1986).
4. T. P. Su, E. D. London, J. H. Jaffe, *Science* **240**, 219 (1988).
5. R. A. Wilke *et al.*, *J. Physiol.* **517**, 391 (1999).
6. R. A. Glennon *et al.*, *J. Med. Chem.* **37**, 1214 (1994).
7. F. F. Moebius, R. J. Reiter, M. Hanner, H. Glossmann, *Br. J. Pharmacol.* **121**, 1 (1997).
8. S. A. Barker, J. A. Monti, S. T. Christian, *Int. Rev. Neurobiol.* **22**, 83 (1981).
9. F. Franzen, H. Gross, *Nature* **206**, 1052 (1965).
10. M. S. Jacob, D. E. Presti, *Med. Hypotheses* **64**, 930 (2005).
11. J. Axelrod, *Science* **134**, 343 (1961).
12. J. M. Saavedra, J. Axelrod, *Science* **175**, 1365 (1972).
13. J. M. Beaton, P. E. Morris, *Mech. Ageing Dev.* **25**, 343 (1984).
14. S. A. Burchett, T. P. Hicks, *Prog. Neurobiol.* **79**, 223 (2006).
15. B. Borowsky *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 8966 (2001).
16. L. Lindemann *et al.*, *Genomics* **85**, 372 (2005).
17. J. R. Kahoun, A. E. Ruoho, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 1393 (1992).
18. A. Pal *et al.*, *Mol. Pharmacol.* **72**, 921 (2007).
19. Y. Chen, A. R. Hajipour, M. K. Sievert, M. Arbabian, A. E. Ruoho, *Biochemistry* **46**, 3532 (2007).
20. P. J. Lupardus *et al.*, *J. Physiol.* **526**, 527 (2000).
21. H. Zhang, J. Cuevas, *J. Pharmacol. Exp. Ther.* **313**, 1387 (2005).
22. E. Aydar, C. P. Palmer, V. A. Klyachko, M. B. Jackson, *Neuron* **34**, 399 (2002).
23. R. A. Wilke *et al.*, *J. Biol. Chem.* **274**, 18387 (1999).
24. C. Kennedy, G. Henderson, *Neuroscience* **35**, 725 (1990).
25. H. Zhang, J. Cuevas, *J. Neurophysiol.* **87**, 2867 (2002).
26. M. A. Johannessen, A. Ramos-Serrano, S. Ramachandran, A. E. Ruoho, M. B. Jackson, "Sigma receptor modulation of voltage-dependent sodium channels," Program No. 466.22, Annual Neuroscience Meeting, San Diego, CA, 5 November 2007.
27. F. Langa *et al.*, *Eur. J. Neurosci.* **18**, 2188 (2003).
28. P. Jenner, C. D. Marsden, C. M. Thanki, *Br. J. Pharmacol.* **69**, 69 (1980).
29. R. R. Matsumoto, B. Pouw, *Eur. J. Pharmacol.* **401**, 155 (2000).
30. T. Hayashi, T. P. Su, *Cell* **131**, 596 (2007).

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Supporting Online Material

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Materials and Methods
Fig. S1 and scheme S2
References

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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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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

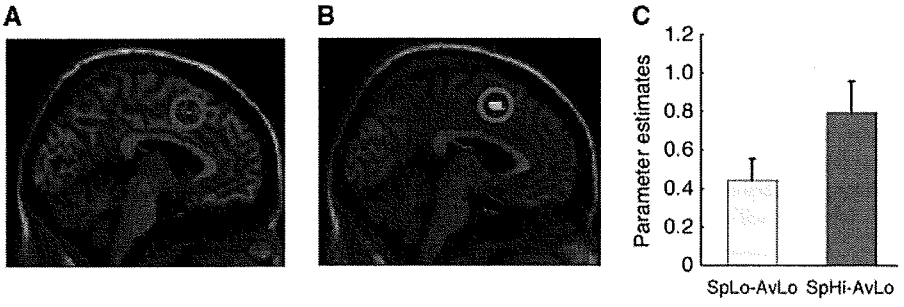

Fig. 1. Brain activation in dACC was modulated by relevance of comparison domain. Brain activations in response to **(A)** the SpLo minus AvLo condition and **(B)** the SpHi minus AvLo condition. **(C)** Mean for parameter estimates at the peak of dACC activation for SpHi-AvLo contrast (red) was greater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

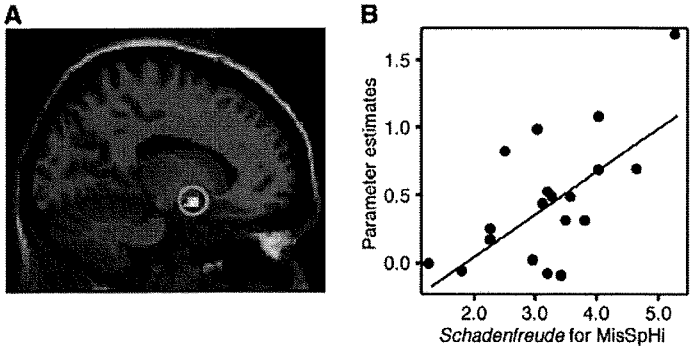

Fig. 2. Correlation between self-rating of schadenfreude and ventral striatum activation across participants. **(A)** Image showing correlation between mean rating of schadenfreude for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. **(B)** Plots and regression line 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.

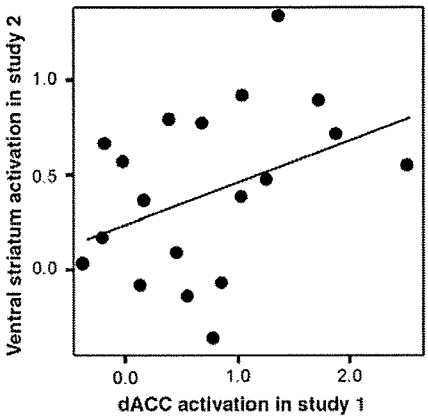

Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (–2, 10, 52). The y axis indicates the parameter estimates of the ventral 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 nonenvied 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*).

References and Notes

1. B. Russell, *The Conquest of Happiness* (W.W. Norton, New York, 1930).
2. Aristotle, *The Art of Rhetoric* (Penguin Books, London, 1981).
3. W. G. Parrott, R. H. Smith, *J. Pers. Soc. Psychol.* **64**, 906 (1993).
4. R. H. Smith, W. G. Parrott, E. F. Diener, R. H. Hoyle, S. H. Kim, *Pers. Soc. Psychol. Bull.* **25**, 1007 (1999).
5. A. Tesser, *Adv. Exp. Soc. Psychol.* **21**, 181 (1988).
6. J. Rawls, *A Theory of Justice* (Harvard Univ. Press, Cambridge, MA, 1971).
7. R. Nozick, *Anarchy, State, and Utopia* (Basic Books, New York, 1974).
8. G. F. de la Mora, *Egalitarian Envy: The Political Foundations of Social Justice* (Paragon House, New York, 1987).
9. D. Hume, *A Treatise of Human Nature* (Oxford Univ. Press, Oxford, 1978).
10. L. Festinger, *Hum. Relat.* **7**, 117 (1954).
11. N. Eisenberg, *Novartis Found. Symp.* **278**, 71 (2007).
12. T. Singer *et al.*, *Science* **303**, 1157 (2004).
13. F. Heider, *The Psychology of Interpersonal Relations* (Wiley & Sons, New York, 1958).
14. B. de Spinoza, *The Ethics* (Biblio Bazaar, Charleston, SC, 2006).
15. W. W. van Dijk, J. W. Ouwerkerk, S. Goslinga, M. Nieweg, M. Gallucci, *Emotion* **6**, 156 (2006).
16. A. Tesser, D. Cornell, *J. Exp. Soc. Psychol.* **27**, 501 (1991).
17. D. M. Amodio *et al.*, *Psychol. Sci.* **15**, 88 (2004).
18. E. Harmon-Jones, *Biol. Psychol.* **67**, 51 (2004).
19. J. G. Kerns *et al.*, *Science* **303**, 1023 (2004).
20. N. I. Eisenberger, M. D. Lieberman, K. D. Williams, *Science* **302**, 290 (2003).
21. J. D. Greene, R. B. Sommerville, L. E. Nystrom, J. M. Darley, J. D. Cohen, *Science* **293**, 2105 (2001).
22. T. Sharot, A. M. Riccardi, C. M. Raio, E. A. Phelps, *Nature* **450**, 102 (2007).
23. Materials and methods are available as supporting material on *Science* Online.
24. E. Lazear, *J. Polit. Econ.* **97**, 561 (1989).
25. S. M. McClure, M. K. York, P. R. Montague, *Neuroscientist* **10**, 260 (2004).
26. E. Fehr, C. F. Camerer, *Trends Cogn. Sci.* **11**, 419 (2007).
27. D. J.-F. de Quervain *et al.*, *Science* **305**, 1254 (2004).
28. T. Singer *et al.*, *Nature* **439**, 466 (2006).
29. K. Fliessbach *et al.*, *Science* **318**, 1305 (2007).

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Impact of changing the Japanese term for "schizophrenia" for reasons of stereotypical beliefs of schizophrenia in Japanese youth

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ABSTRACT

The old term for schizophrenia, "Seishin-Bunretsu-Byo" (Mind-Split Disease), has been replaced by "Togo-Shitcho-Sho" (Integration Disorder) in Japan. Stigma research requiring individuals to report personal beliefs is useful but is subject to social desirability bias. Using the Implicit Association Test, a measurement designed to minimize this bias, we assessed the impact of this renaming on the stereotype of schizophrenia held by a younger generation. The old term was strongly associated with "criminal", and this association became significantly weaker with the new term. The strategy of renaming holds considerable promise for tempering negative bias toward this disorder in Japan.

1. Introduction

The stigma of mental disorders stands in the way of improving the quality of life of people with disorders as well as their families. The stigma leads to discriminations in education, employment, personal relationships, marriage and housing. To reduce mental illness-related stigma (particularly regarding schizophrenia), various programs are underway internationally (Sartorius, 2007; Thornicroft et al., 2007). In Japan as well, a strategy to change the term for schizophrenia was introduced. Since each Chinese character conveys its own meaning, and the old term for schizophrenia, "Seishin-Bunretsu-Byo", explicitly translates as "Mind-Split-Disease", the Japanese Society of Psychiatry and Neurology approved replacing the old term with "Togo-Shitcho-Sho", literally meaning "Integration Disorder". The former term has been said to lead the public to misunderstand and stigmatize individuals with schizophrenia.

In western society, the term also implies "split" and is frequently misunderstood as "split personality" (Chopra and Doody, 2007) or inappropriately metaphorized (Geller, 2001). In fact, even in a renowned scientific journal, "schizophrenia" was recently misused as "split personality" (May, 2008; Pfleiderer and Hackl, 2007). Thus, movements to rename schizophrenia are gaining momentum in western society as well (Kingdon et al., 2007). Most stigma research relies on questionnaires that require individuals to report their personal attitude (Greenwald and Banaji, 1995; Hinshaw and Stier, 2008). This information is useful but is subject to response bias due to social desirability (Dovidio et al., 1997;

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Gaebel et al., 2002; Griffiths et al., 2006; Hinshaw and Stier, 2008). One measure designed to minimize response bias is the Implicit Association Test (IAT) (Greenwald et al., 1998). IAT assesses associations that exist beyond conscious evaluation, allowing a measurement of automatic biases even if people are unaware or unwilling to report them. This method has been widely used to assess implicit attitudes and stereotypes associated with many characteristics, including age, race and gender (Greenwald et al., 2002). Recently, IAT has been applied to the assessment of negative attitude toward mental illness (Teachman et al., 2006). Using IAT, we assessed the impact of renaming on the implicit stigma associated with this disorder in Japan. The most prevalently held stereotype is that of people with mental illness being unpredictable and dangerous (Angermeyer and Matschinger, 2004). The media are an important source of public information on mental illness (Stark et al., 2004), and negative depictions (criminality and dangerousness) of mental illness predominate (Coverdale et al., 2002). The media tend to present sensationalized and stereotypic depictions of mental illness and emphasize propensities toward violence and crime (Hinshaw and Stier, 2008). However, previous studies have revealed that people with mental illness are far more likely to be victims of crime than perpetrators (Hinshaw and Stier, 2008; Teplin et al., 2005). We assessed the association between schizophrenia and criminal versus victim. We hypothesized that the new term would have less automatic association with criminal.

2. Materials and methods

2.1. Participants

Sixty-eight non-medical undergraduate students (28 males and 40 females, mean age 21.5 years, S.D. = 1.4) participated. All were Japanese. They were asked if they were aware of the replacement of the term for schizophrenia. They were further asked about their knowledge of schizophrenia using a 7-point scale (1= none, 7= very much). The average score of knowledge was 3.5, indicating that the participants did not have enough or accurate knowledge of schizophrenia, although the majority (88%) knew of the renaming from the media. After complete explanation of the study, written informed consent was obtained from all participants, and the study was approved by the Ethics Committee.

2.2. Measures and procedures

To assess explicit attitudes, participants reported their attitude about mental illness using the Japanese version of the 4-point Link's devaluation–discrimination-scale (Link, 1987; Shimotsu et al., 2006), a 12-item scale that has been widely used to measure stigma in relation to mental illness. Each item is designed to report what a subject thinks most people's opinion is concerning mental illness rather than to report the subject's own opinion. The items include, for example, "Most people think less of a person who has been in a mental hospital." Each statement is rated on a 4-point scale ranging from "strongly disagree = 1" to "strongly agree = 4", yielding a total score from 12 to 48.

To assess the automatic association between schizophrenia and criminal, IAT was administered according to standard procedures (Greenwald et al., 1998). Briefly, a physical chronic illness, diabetes mellitus, was used for comparison, since schizophrenia is a generally chronic illness, and awareness of comorbid diabetes in schizophrenia has been increasing with the introduction of atypical antipsychotics. The associations of these illnesses with two attributes (criminal and victim) were assessed. We conducted an initial survey to select target words associated with schizophrenia, diabetes, criminal and victim. Twenty university students other than the participants of this study were screened. They were asked to come up with up to 30 words associated with each of schizophrenia, diabetes, criminal and victim. We selected the most commonly proposed 10 words for each. Then an experienced psychologist (TI), who was a trained experimenter of IAT, and two experienced psychiatrists (HT and MK) assessed the selected words in terms of word length, complexity, familiarity and clarity. Five words for each category meeting a consensus were finally selected. Schizophrenia (hallucination, delusion, psychiatry, bizarre, seclusion), diabetes (obesity, insulin, diet, sugar, internal medicine), criminal (violence, jail, murder, theft, robbery) and victim (disaster, family, accident, casualty, the bereaved) stimuli appeared in the center of the computer screen. In congruent condition (CC), the concept "schizophrenia" and attribute "criminal" were paired in the top left corner while "diabetes" and "victim" were simultaneously paired in the top right corner. Participants were told to classify any stimuli that belonged to either the schizophrenia or criminal categories on the left, and any that belonged to either the diabetes or victim categories on the right, as quickly as possible by pressing a left or right button. In incongruent condition (IC), the labels were switched and the same categorization task was completed while pairing "schizophrenia" with "victim" and "diabetes" with "criminal". There were 40 trials for both CC and IC. Since negative attitudes toward mental illness are observed in many cultures (Kadri and Sartorius, 2005), it was predicted that CC categorizations would be easier and thus made more quickly than IC ones. Strong implicit associations should lead to fast congruent and slow incongruent categorizations. As a result, the IAT effect (reaction time for IC minus CC) provides a measure of the strength of implicit associations. To examine the impact of changing the term for schizophrenia, 2 versions of IAT were run for each participant. The old term for schizophrenia was used in one version, and the new term in the other version. The order of the two versions was counterbalanced across the subjects.

3. Results

The average total score of Link's devaluation–discrimination-scale was 31.9 (S.D. = 5.5). This was in very good agreement with the study of reliability and validity of the Japanese translated version, in which the average total scores for males and females were 31.6 and 31.9, respectively (Shimotsu et al., 2006).

For the "Seishin-Bunretsu-Byo" version, average response latency for CC and IC was 844 ms (SEM = 21) and 927 ms (SEM = 25), respectively, yielding an 84-ms averaged IAT effect. For the "Togo-Shitcho-Sho" version, average response latency for CC and IC was 871 ms (SEM = 24) and 892 ms (SEM = 23), respectively, yielding a 21-ms averaged IAT effect.

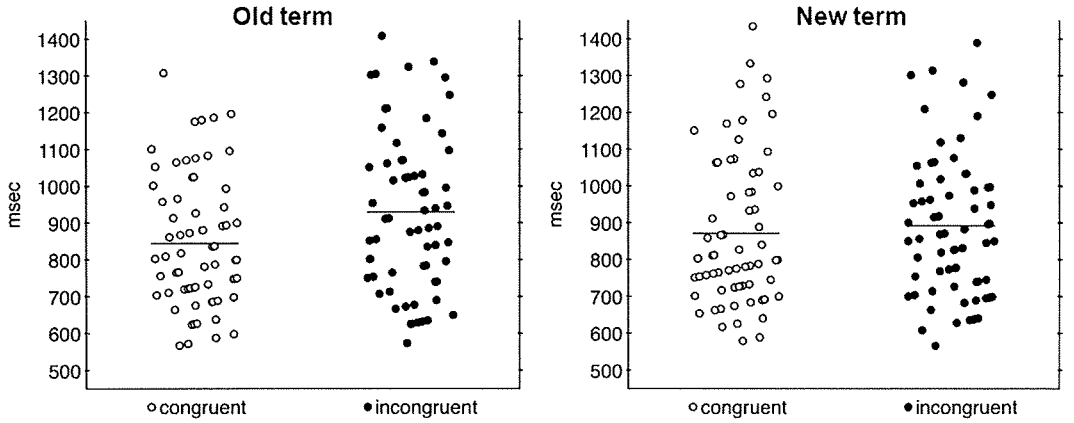

Fig. 1. Average response latency for CC and IC in old- and new-term versions of IAT. White dots indicate CC and black dots indicate IC. The bars represent the mean response latency of each condition. ANOVA revealed that response latencies were significantly longer for old term than for new term in IC, but that there was no significant difference in response latencies between old and new in CC.

Response latencies were analysed by a 3-way analysis of variance (ANOVA) with term (old term vs. new term) and condition (CC vs. IC) as within-subject factors and gender as between-subject factors. ANOVA yielded a significant condition main effect, $F(1, 66) = 15.6$, $p<0.001$, and a significant interaction between term and condition, $F(1, 66) = 8.6$, $p<0.005$. There was neither significant term main effect ($F(1, 66) = 0.15$) nor gender main effect (F (1, 66) = 0.60). There was neither significant interaction between term and gender (F (1, 66) = 0.35) nor between condition and gender ($F(1, 66) = 0.03$).

The significant interaction effect was explored further using a simple main effects analysis, which revealed that response latencies were significantly longer ($p = 0.03$) for the old term than for the new term in IC. In CC, there was no significant difference in response latencies between the old and new terms. Response latencies were significantly longer ($p<0.001$) for IC than for CC in the old term experiment, but not in the new term experiment (Fig. 1). There were loose negative correlations between explicit Link's scale and IAT effect for both the new and old terms ($r = -0.252$, $p<0.05$ and $r = -0.281$, $p<0.05$ respectively). There was no significant correlation between explicit Link's scale and other IAT measures (response latencies for CC and IC).

4. Discussion

The current study demonstrated that the old term "Seishin-Bunretsu-Byo" (Mind-Split Disease) was more incongruent with victims than the new term "Togo-Shitcho-Sho" (Integration Disorder), suggesting that the old term was strongly associated with "criminal" vs. "victims", while the automatic association between the new term and criminal was not strong. There was no positive significant correlation between the explicit Link's scale and IAT measures. On the contrary, a loose negative correlation between Link's scale and IAT effect was observed. The lack of positive correlation was expected, but the negative correlation was an unexpected result. Although we do not have precise explanations, several factors might have contributed to this result. Link's scale is intended for mental illness in general, not only for schizophrenia, and it assesses what a subject thinks most people think about mental illness rather than report the subject's own opinion. What the subject believes personally and what the subject thinks most people believe might have been different. Moreover, explicit measures are said to possibly be influenced by social desirability bias (Dovidio et al., 1997; Gaebel et al., 2002; Griffiths et al., 2006; Hinshaw and Stier, 2008). Thus, our result suggested the importance of implicit measures in addition to explicit measures in the field of stigma research (Thornicroft et al., 2007). The IAT results indicated that the strategy of renaming seemed successful for tempering the negative bias toward this disorder in Japan. Obviously, it might be superficial and not deal with the root cause of stigma (Lieberman and First, 2007). Still, our results showed that words play some role in the creation of negative images.

The current study has some limitations. First, we did not survey a larger group, systematically, from a wide range of decades. Generational differences in the effect of renaming would be another important topic needing investigation in future studies, as older people would have a longer history with the old term and stigma, and discrimination toward mental illness would have been more evident when they were young. Second, we investigated only the association between schizophrenia and criminal using diabetes as control illness. There are prevalent stereotypes other than "criminal, dangerous and violent" that contribute to stigma for schizophrenia, e.g. incompetent (Hinshaw and Stier, 2008). Further IAT studies to investigate the association between schizophrenia and other stereotypical attributes using different control illnesses are recommended. Finally, the knowledge concerning schizophrenia was assessed using the participants' self-evaluation of their knowledge about schizophrenia. Future studies will require tools with greater objectivity for assessing knowledge of schizophrenia and examine the effect of knowledge or experience on attitudes toward schizophrenia. We hope that this report will stimulate discussion concerning renaming not only in several Asian areas where identical Chinese characters are used for "schizophrenia", but also in western societies.

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Contributors

Author Takahashi and Ideno designed the study and wrote the protocol. Author Takahashi and Ideno managed the literature searches and analyses. Authors Ideno, Okubo S. and Matsui undertook the statistical analysis, and author Takahashi wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

The authors have no conflict of interest.

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References

Angermeyer, M.C., Matschinger, H., 2004. The stereotype of schizophrenia and its impact on discrimination against people with schizophrenia: results from a representative survey in Germany. Schizophr. Bull. 30 (4), 1049–1061.

Chopra, A.K., Doody, G.A., 2007. Schizophrenia, an illness and a metaphor: analysis of the use of the term "schizophrenia" in the UK national newspapers. J. R. Soc. Med. 100 (9), 423–426.

Coverdale, J., Nairn, R., Claasen, D., 2002. Depictions of mental illness in print media: a prospective national sample. Aust. N. Z. J. Psychiatry 36 (5), 697–700.

Dovidio, J., Kawakami, K., Johnson, C., Johnson, B., Howard, A., 1997. On the nature of prejudice: automatic and controlled processes. J. Exp. Soc. Psychol. 33 (5), 510–540.

Gaebel, W., Baumann, A., Witte, A.M., Zaeske, H., 2002. Public attitudes towards people with mental illness in six German cities: results of a public survey under special consideration of schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 252 (6), 278–287.

Geller, J.L., 2001. Ain't no such thing as a schizophrenic. Psychiatr. Serv. 52 (6), 715.

Greenwald, A., Banaji, M., 1995. Implicit social cognition: attitudes, self-esteem, and stereotypes. Pyschol. Rev. 102, 4–27.

Greenwald, A.G., McGhee, D.E., Schwartz, J.L., 1998. Measuring individual differences in implicit cognition: the implicit association test. J. Pers. Soc. Psychol. 74 (6), 1464–1480.

Greenwald, A.G., Banaji, M.R., Rudman, L.A., Farnham, S.D., Nosek, B.A., Mellott, D.S., 2002. A unified theory of implicit attitudes, stereotypes, self-esteem, and self-concept. Psychol. Rev. 109 (1), 3–25.

Griffiths, K.M., Nakane, Y., Christensen, H., Yoshioka, K., Jorm, A.F., Nakane, H., 2006. Stigma in response to mental disorders: a comparison of Australia and Japan. BMC Psychiatry 6, 21.

Hinshaw, S.P., Stier, A., 2008. Stigma as related to mental disorders. Annu. Rev. Clin. Psychol. 4, 367–393.

Kadri, N., Sartorius, N., 2005. The global fight against the stigma of schizophrenia. PLoS Med. 2 (7), e136.

Kingdon, D.G., Kinoshita, Y., Naeem, F., Swelam, M., Hansen, L., Vincent, S., Rathod, S., 2007. Schizophrenia can and should be renamed. BMJ 334 (7587), 221–222.

Lieberman, J.A., First, M.B., 2007. Renaming schizophrenia. BMJ 334 (7585), 108.

Link, B., 1987. Understanding labeling effects in the area of mental disorders: an assessment of the effects of expectations of rejection. Am. Sociol. Rev. 52 (1), 96–112.

May, A.C., 2008. Schizophrenia does not mean split personality. Nature 451 (7175), 127.

Pfleiderer, C., Hackl, R., 2007. High-temperature superconductivity: schizophrenic electrons. Nature 450 (7169), 492–493.

Sartorius, N., 2007. Stigma and mental health. Lancet 370 (9590), 810–811.

Shimotsu, S., Sakamoto, S., Horikawa, N., Sakano, Y., 2006. Reliability and validity of the Japanese version of Link's devaluation–discrimination scale. Seisinka Chiryogaku 21 (5), 521–528.

Stark, C., Paterson, B., Devlin, B., 2004. Newspaper coverage of a violent assault by a mentally ill person. J. Psychiatr. Ment. Health Nurs. 11 (6), 635–643.

Teachman, B., Wilson, J., Komarovskaya, I., 2006. Implicit and explicit stigma of mental illness in diagnosed and healthy samples. J. Soc. Clin. Psychol. 25 (1), 75–95.

Teplin, L.A., McClelland, G.M., Abram, K.M., Weiner, D.A., 2005. Crime victimization in adults with severe mental illness: comparison with the National Crime Victimization Survey. Arch. Gen. Psychiatry 62 (8), 911–921.

Thornicroft, G., Rose, D., Kassam, A., Sartorius, N., 2007. Stigma: ignorance, prejudice or discrimination? Br. J. Psychiatry 190, 192–193.

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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 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.

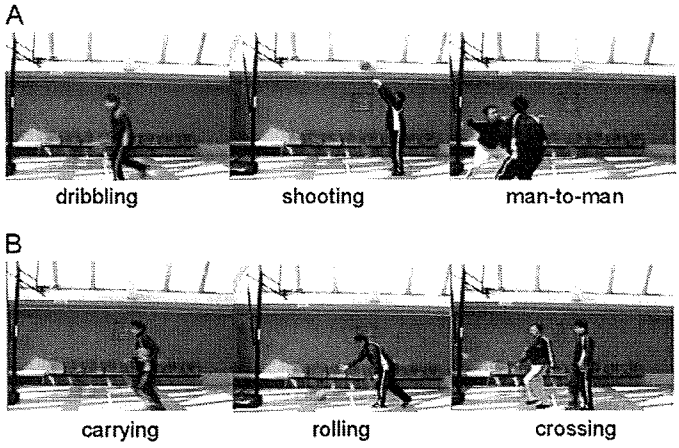

Fig. 1. Sample of Still Frames From Video Clips. A, Basketball-related motions; B, basketball-unrelated motions.

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.

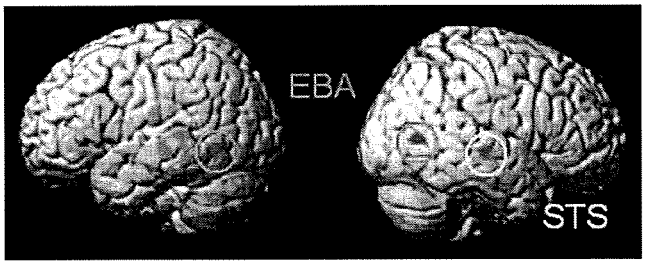

Fig. 2. Images Showing the Brain Area of Diminished Activations in Response to Basketball-Related Motions (BRM) Relative to Basketball-Unrelated Motions (BUM) Condition in 12 Patients With Schizophrenia Compared With 12 Normal Controls. Diminished activations in the bilateral extrastriate body area (EBA),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

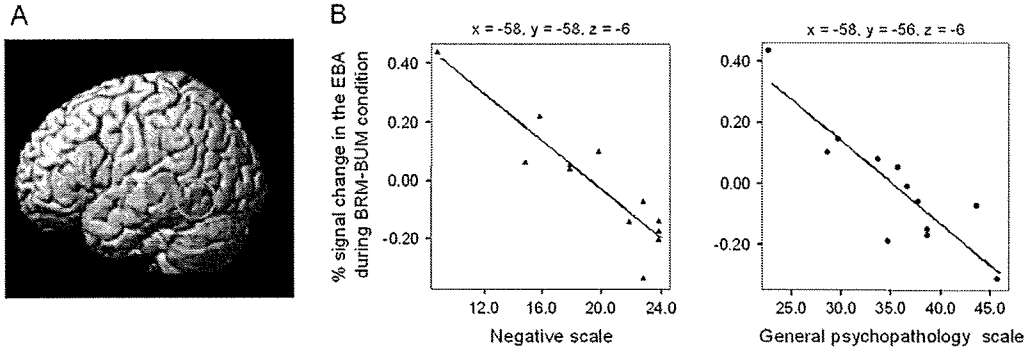

Fig. 3. Negative Correlations Between Positive and Negative Syndrome Scale (PANSS) Scores and the Degree of Activation in the Extrastriate Body area (EBA). A, Images showing negative correlation between negative scale scores and the degree of activation in the left EBA in basketball-related motions-basketball-unrelated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

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References

1. Henderson DC. Diabetes mellitus and other metabolic disturbances induced by atypical antipsychotic agents. *Curr Diab Rep.* 2002;2:135–140.
2. Menza M, Vreeland B, Minsky S, Gara M, Radler DR, Sakowitz M. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. *J Clin Psychiatry.* 2004;65:471–477.
3. Langle G, Siemssen G, Hornberger S. Role of sports in treatment and rehabilitation of schizophrenic patients. *Rehabilitation (Stuttg).* 2000;39:276–282.
4. Daumit GL, Goldberg RW, Anthony C, et al. Physical activity patterns in adults with severe mental illness. *J Nerv Ment Dis.* 2005;193:641–646.
5. Faulkner G, Cohn T, Remington G. Validation of a physical activity assessment tool for individuals with schizophrenia. *Schizophr Res.* 2006;82:225–231.
6. Boks MP, Russo S, Knegtering R, van den Bosch RJ. The specificity of neurological signs in schizophrenia: a review. *Schizophr Res.* 2000;43:109–116.
7. Kodama S, Fukuzako H, Fukuzako T, et al. Aberrant brain activation following motor skill learning in schizophrenic patients as shown by functional magnetic resonance imaging. *Psychol Med.* 2001;31:1079–1088.
8. Weickert TW, Terrazas A, Bigelow LB, et al. Habit and skill learning in schizophrenia: evidence of normal striatal processing with abnormal cortical input. *Learn Mem.* 2002;9:430–442.
9. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci.* 1986;9:357–381.
10. Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry.* 1999;56:781–787.
11. Grezes J, Decety J. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. *Hum Brain Mapp.* 2001;12:1–19.
12. Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. *Nat Rev Neurosci.* 2006; 7:942–951.
13. Chartrand TL, Bargh JA. The chameleon effect: the perception-behavior link and social interaction. *J Pers Soc Psychol.* 1999;76:893–910.
14. Brass M, Heyes C. Imitation: is cognitive neuroscience solving the correspondence problem? *Trends Cogn Sci.* 2005; 9:489–495.
15. Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. *Trends Cogn Sci.* 2000;4:267–278.
16. Frith U, Frith CD. Development and neurophysiology of mentalizing. *Philos Trans R Soc Lond B Biol Sci.* 2003;358:459–473.
17. Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. *Trends Cogn Sci.* 2003;7:77–83.
18. Kim J, Doop ML, Blake R, Park S. Impaired visual recognition of biological motion in schizophrenia. *Schizophr Res.* 2005;77:299–307.
19. Downing PE, Jiang Y, Shuman M, Kanwisher N. A cortical area selective for visual processing of the human body. *Science.* 2001;293:2470–2473.
20. Peelen MV, Wiggett AJ, Downing PE. Patterns of fMRI activity dissociate overlapping functional brain areas that respond to biological motion. *Neuron.* 2006;49:815–822.
21. Astafiev SV, Stanley CM, Shulman GL, Corbetta M. Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nat Neurosci.* 2004;7:542–548.
22. Jackson PL, Meltzoff AN, Decety J. Neural circuits involved in imitation and perspective-taking. *Neuroimage.* 2006;31:429–439.
23. Takahashi H, Shibuya T, Kato M, et al. Enhanced activation in the extrastriate body area by goal-directed actions. *Psychiatry Clin Neurosci.* 2008;62:214–219.
24. Torrey EF. Schizophrenia and the inferior parietal lobule. *Schizophr Res.* 2007;97:215–225.
25. Rey MJ, Schulz P, Costa C, Dick P, Tissot R. Guidelines for the dosage of neuroleptics. I: Chlorpromazine equivalents of orally administered neuroleptics. *Int Clin Psychopharmacol.* 1989;4:95–104.
26. Rijcken CA, Monster TB, Brouwers JR, de Jong-van den Berg LT. Chlorpromazine equivalents versus defined daily doses: how to compare antipsychotic drug doses? *J Clin Psychopharmacol.* 2003;23:657–659.
27. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261–276.
28. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage.* 2003; 19:1233–1239.
29. Arzy S, Thut G, Mohr C, Michel CM, Blanke O. Neural basis of embodiment: distinct contributions of temporoparietal junction and extrastriate body area. *J Neurosci.* 2006;26:8074–8081.
30. Puce A, Perrett D. Electrophysiology and brain imaging of biological motion. *Philos Trans R Soc Lond B Biol Sci.* 2003; 358:435–445.
31. Russell TA, Reynaud E, Herba C, Morris R, Corcoran R. Do you see what I see? Interpretations of intentional movement in schizophrenia. *Schizophr Res.* 2006;81:101–111.
32. Jeannerod M. Visual and action cues contribute to the self-other distinction. *Nat Neurosci.* 2004;7:422–423.
33. Cheng Y, Meltzoff AN, Decety J. Motivation modulates the activity of the human mirror-neuron system. *Cereb Cortex.* 2007;17:1979–1986.
34. Danckert J, Rossetti Y, d'Amato T, Dalery J, Saoud M. Exploring imagined movements in patients with schizophrenia. *Neuroreport.* 2002;13:605–609.
35. Maruff P, Wilson P, Currie J. Abnormalities of motor imagery associated with somatic passivity phenomena in schizophrenia. *Schizophr Res.* 2003;60:229–238.
36. Calvo-Merino B, Glaser DE, Grezes J, Passingham RE, Haggard P. Action observation and acquired motor skills: an FMRI study with expert dancers. *Cereb Cortex.* 2005;15:1243–1249.
37. Ertelt D, Small S, Solodkin A, et al. Action observation has a positive impact on rehabilitation of motor deficits after stroke. *Neuroimage.* 2007;36(Suppl. 2):T164–173.
38. Okubo Y, Olsson H, Ito H, et al. PET mapping of extrastriatal D2-like dopamine receptors in the human brain using an anatomic standardization technique and [11C]FLB 457. *Neuroimage.* 1999;10:666–674.

Behavioral/Systems/Cognitive

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 doparminergic drug therapy such as levodopa 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-[^{18}F]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.

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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,

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 $2 \times 2 \times 2$ mm^3. 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 [^{11}C]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 [^{11}C]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 [^{11}C]SCH23390 and 90 min for [^{11}C]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: $BP_{ND} = k_3/k_4 = f_2 B_{max}/\{K_d [1 + \Sigma_i F_i/K_{di}]\}$, where k_3 and k_4 describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, f_2 is the "free fraction" of nonspecifically bound radioligand in brain, B_{max} is the receptor density, K_d is the equilibrium dissociation constant for the radioligand, and F_i and K_{di} are the free concentration and dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996). Tissue concentrations of the radioactivities of [^{11}C]SCH23390 and [^{11}C]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 [^{11}C]SCH23390 and [^{11}C]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 [^{11}C]SCH23390 and [^{11}C]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 outgroup), 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

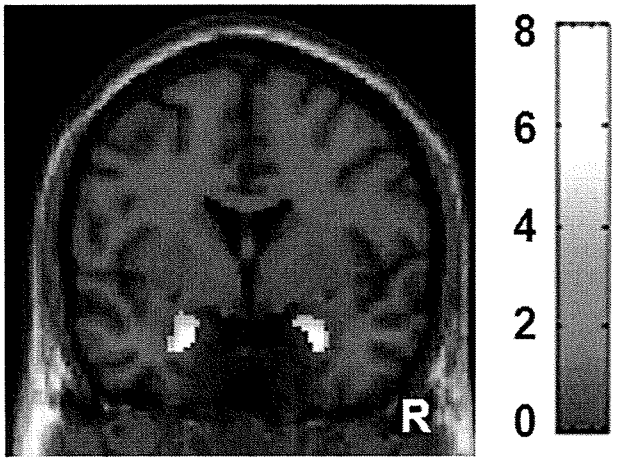

Figure 1. Images showing brain response induced by fear and neutral minus baseline condition. Bilateral amygdala responses are shown. The bar shows the range of the *t*-value. R indicates right.

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 functional ROIs defined by fMRI 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.

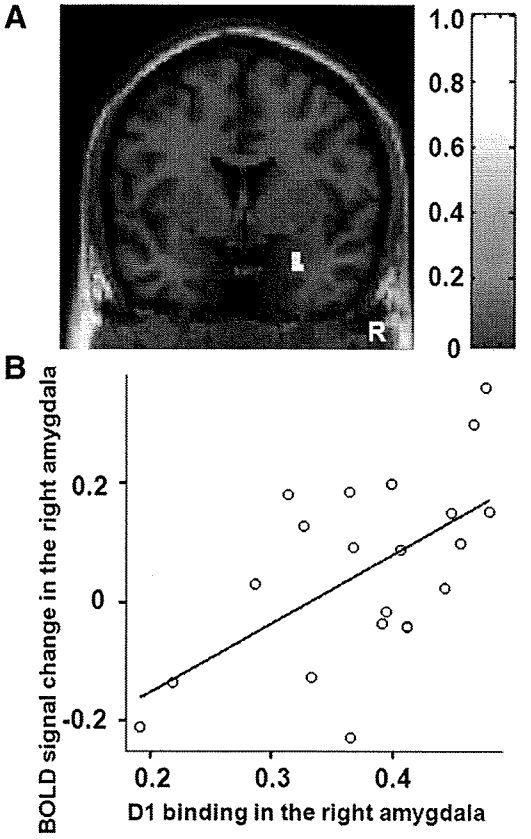

Figure 2. *A*, SPM correlation analysis revealed significant positive linear correlations between D1 binding in the right amygdala and right amygdala signal change. The bar shows the range of the correlation coefficient. *B*, ROI correlation analysis also revealed similar correlations. R indicates right.

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 expression. 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 [^{11}C]SCH23390 and [^{11}C]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).

References

Abi-Dargham A, Simpson N, Kegeles L, Parsey R, Hwang DR, Anjilvel S, Zea-Ponce Y, Lombardo I, Van Heertum R, Mann JJ, Foged C, Halldin C, Laruelle M (1999) PET studies of binding competition between endogenous dopamine and the D1 radiotracer [^{11}C] NNC 756. Synapse 32:93–109.

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

Bissière S, Humeau Y, Lüthi A (2003) Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition. Nat Neurosci 6:587–592.

Brett M, Anton J, Valabregue R, Poline J (2002) Region of interest analysis using the MarsBar toolbox [abstract]. Paper presented at 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Casanova R, Srikanth R, Baer A, Laurienti PJ, Burdette JH, Hayasaka S, Flowers L, Wood F, Maldjian JA (2007) Biological parametric mapping: a statistical toolbox for multimodality brain image analysis. Neuroimage 34:137–143.

Cervenka S, Pålhagen SE, Comley RA, Panagiotidis G, Cselényi Z, Matthews JC, Lai RY, Halldin C, Farde L (2006) Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. Brain 129:2017–2028.

Chou YH, Karlsson P, Halldin C, Olsson H, Farde L (1999) A PET study of D1-like dopamine receptor ligand binding. Psychopharmacology 146:220–227.

Convit A, McHugh P, Wolf OT, de Leon MJ, Bobinski M, De Santi S, Roche A, Tsui W (1999) MRI volume of the amygdala: a reliable method allowing separation from the hippocampal formation. Psychiatry Res 90:113–123.

de la Mora MP, Gallegos-Cari A, Arizmendi-Garcia Y, Marcellino D, Fuxe K (2009) Role of dopamine receptor mechanisms in the amygdaloid modulation of fear and anxiety: structural and functional analysis. Prog Neurobiol. Advance online publication. Retrieved October 21, 2009. doi:10.1016/j.pneurobio.2009.10.010.

Drevets WC (2000) Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog Brain Res 126:413–431.

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

Farde L, Hall H, Pauli S, Halldin C (1995) Variability in D2-dopamine receptor density and affinity: a PET study with [^{11}C] raclopride in man. Synapse 20:200–208.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997) Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 6:279–287.

Hariri AR, Mattay VS, Tessitore A, Fera F, Smith WG, Weinberger DR (2002) Dextroamphetamine modulates the response of the human amygdala. Neuropsychopharmacology 27:1036–1040.

Hart AJ, Whalen PJ, Shin LM, McInerney SC, Fischer H, Rauch SL (2000) Differential response in the human amygdala to racial outgroup vs ingroup face stimuli. Neuroreport 11:2351–2355.

Inglis FM, Moghaddam B (1999) Dopaminergic innervation of the amygdala is highly responsive to stress. J Neurochem 72:1088–1094.

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

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