Table 3
著者らが作成した"日本版後悔・追求者尺度"の因子分析結果(主成分解，バリマックス法)

因子1：後悔(α=.85)		
何かを購入した後に，違うものにしていれば良かったという事がよくある	**.807**	.100
選ぶのに苦労した商品でも，買った後に後悔する事が多い	**.781**	.084
過ぎてしまった事に対して，"こうすれば良かった"などと考える事がよくある	**.739**	−.047
購入した商品が良かったとしても，"もっと良いものもあっただろうに"と思ってしまうことが多い	**.734**	.118
人生において，"あの時こうしておけば良かった"と強く思うことが多い	**.695**	.088
ある商品を購入した際，より良い商品があった可能性を考えて後悔する事がある	**.665**	.056
くよくよ過去の事を悔やむ方だ	**.653**	−.019
自分は優柔不断だと思う	**.502**	.194
因子2：追求者(α=.74)		
可能性がある限り，物事を追求する事に苦労は惜しまない	.158	**.541**
何かの決断をする時は，ありとあらゆる選択肢を考えてみる	.141	**.550**
買い物の時間や，商品を選ぶ時間が他人より長いと思う	.135	**.614**
新しい商品，流行の健康法など，つねに情報収集は欠かさない	.100	**.650**
お気に入りのもの，タレント，歌手などはとことん追求する	.062	**.530**
一つのものを買うにも，他店と比べてみることが多い	.021	**.598**
どんな趣味でも，きわめてみたくなり，没頭するタイプである	.010	**.652**
商品を選ぶ時は，つねに最良のものを選ぶようにしている	−.174	**.626**
因子負荷量の二乗和	4.06	2.93
寄与率(%)	25.4	18.3
累計寄与率(%)	25.4	43.7

引用文献

Allais, M. (1953). Le comportement de l'homme rationnel devant le risque: Critique des postulats et axiomes de l'école américaine. *Econometrica*, **21**, 503-546.

Bell, D. E. (1982). Regret in decision making under uncertainty. *Operations Research*, **30**, 961-981.

Kahneman, D. (2003). Maps of bounded rationality: Psychology for behavioral economics. *American Economic Review*, **93**, 1449-1475.

Loomes, G., & Sugden, R. (1982). Regret theory: An alternative theory of rational choice under uncertainty. *Economic Journal*, **92**, 805-824.

松村 明 (編) (1995). 大辞林 第二版 三省堂
(Matsumura, A.)

von Neumann, J., & Morgenstern, O. (1947). *Theory of games and economic behavior*. 2nd ed. NJ: Princeton University Press.

新村 出 (編) (1998). 広辞苑 第五版 岩波書店
(Niimura, I.)

Savage, L. J. (1951). The theory of statistical decision. *Journal of American Statistical Association*, **46**, 55-67.

Schwartz, B. (2004). The tyranny of choice. *Scientific American*, **290**, 70-75.
(シュワルツ，B. 千葉啓恵・編集部 (訳) (2004). 豊かさが招く不幸 日経サイエンス，7 月号，56-63.)

Schwartz, B., Ward, A., Monterosso, J., Lyubomirsky, S., White, K., & Lehman, D. (2002). Maximizing versus satisficing: Happiness is a matter of choice. *Journal of Personality and Social Psychology*, **83**, 1178-1197.

Simon, H. A. (1955). Behavioral model of rational choice. *Quarterly Journal of Economics*, **69**, 99-118.

竹村和久 (2005). 意思決定現象と行動意思決定論 知能と情報(日本知能情報ファジィ学会誌)，**17**，644-654.
(Takemura, K. (2005). Dicision making and behavioral decision theory. *Journal of Japan Society for Fuzzy Theory and Intelligent Informatics*, **17**, 644-654.)

竹村和久 (2006). リスク社会における判断と意思決定 認知科学，**13**，17-31.
(Takemura, K. (2006). Judgment and decision making in risk society. *Cognitive Studies*, **13**, 17-31.)

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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

www.sciencemag.org/cgi/content/full/323/5916/934/DC1
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

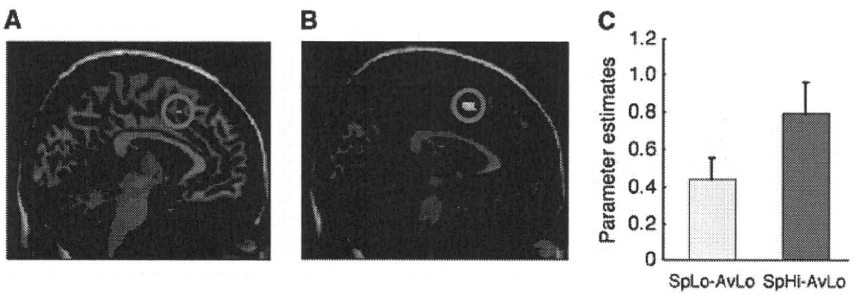

Fig. 1. Brain activation in dACC was modulated by relevance of comparison domain. Brain activations in response to **(A)** the SpLo minus AvLo condition and **(B)** the SpHi minus AvLo condition. **(C)** Mean for parameter estimates at the peak of dACC activation for SpHi-AvLo contrast (red) was greater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

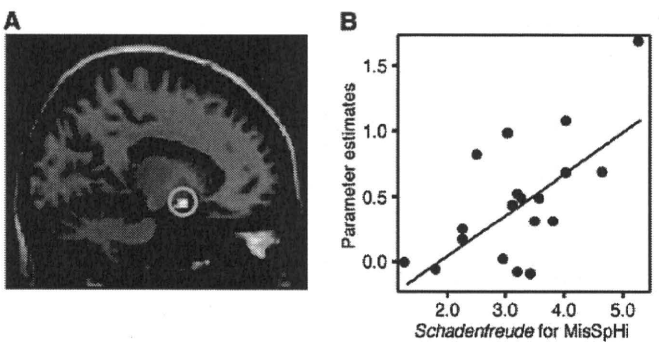

Fig. 2. Correlation between self-rating of schadenfreude and ventral striatum activation across participants. **(A)** Image showing correlation between mean rating of schadenfreude for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. **(B)** Plots and regression line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

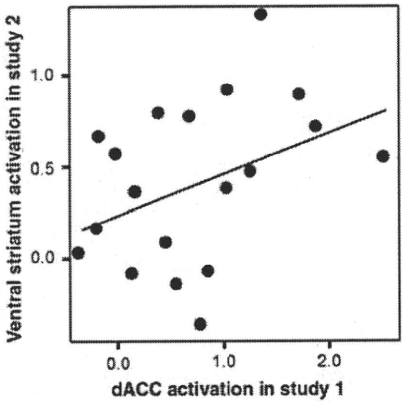

Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (–2, 10, 52). The y axis indicates the parameter estimates of the ventral 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 non-envied person. Between-participant analysis revealed that people with stronger schadenfreude showed greater activation in the ventral striatum.

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

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

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.

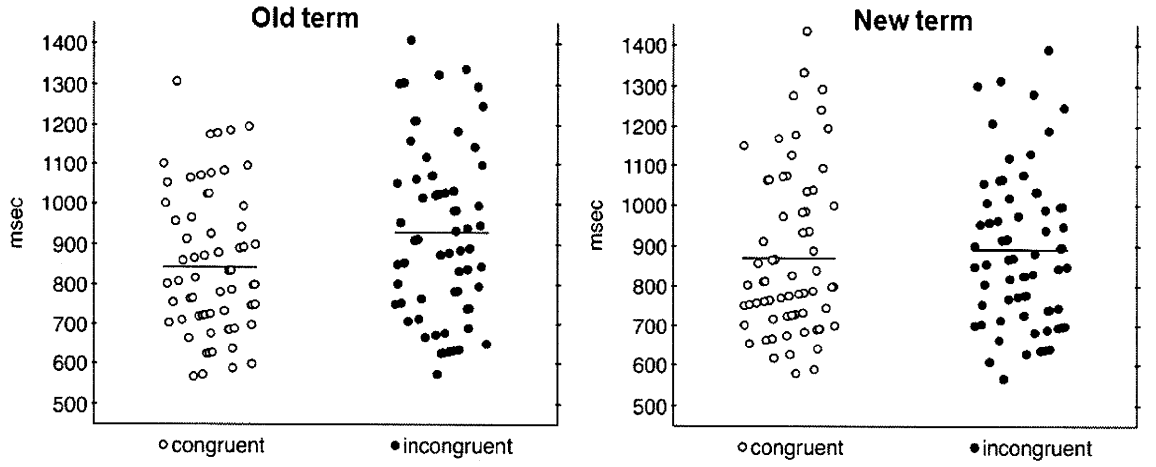

Fig. 1. Average response latency for CC and IC in old- and new-term versions of IAT. White dots indicate CC and black dots indicate IC. The bars represent the mean response latency of each condition. ANOVA revealed that response latencies were significantly longer for old term than for new term in IC, 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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Attitude of young psychiatrists toward coercive measures in psychiatry: a case vignette study in Japan

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Abstract

Background: Every psychiatrist must pay careful attention to avoid violating human rights when initiating coercive treatments such as seclusion and restraint. However, these interventions are indispensable in clinical psychiatry, and they are often used as strategies to treat agitated patients. In this study, we investigated young psychiatrists' attitudes toward psychiatric coercive measures.

Methods: A total of 183 young psychiatrists participated as subjects in our study. A questionnaire with a case vignette describing a patient with acute psychosis was sent to the study subjects via the Internet or by mail. This questionnaire included scoring the necessity for hospitalization, and the likelihood of prescribing seclusion and/or restraint, on a 9-point Likert scale (with 9 indicating strong agreement).

Results: There was general agreement among the study subjects that the case should be admitted to a hospital (8.91 ± 0.3) and secluded (8.43 ± 1.0). The estimated length of hospitalization was 13.53 ± 6.4 weeks. Regarding the likelihood of prescribing restraint, results showed great diversity (5.14 ± 2.5 on 9-point scale); psychiatrists working at general hospitals scored significantly higher (6.25 ± 2.5) than those working at university hospitals (5.02 ± 2.3) or psychiatric hospitals (4.15 ± 2.6). A two-group comparison of the length of inpatient care revealed a significant difference

between those psychiatrists who scored 1-3 (n = 55, 14.22 ± 7.4 wks) and those who scored 7-9 (n = 62, 12.22 ± 4.0) regarding the need to use restraint.

Conclusion: Our results may reflect the current dilemma in Japanese psychiatry wherein psychiatrists must initiate coercive measures to shorten hospitalization stays. This study prompted its subject psychiatrists to consider coercive psychiatric treatments.

Background

There have always been concerns about human rights infringements for coercive psychiatric measures, such as involuntary admission, forced medication, seclusion and/or restraint [1]. Controlled studies have provided no evidence about the validity of such interventions, primarily because ethical considerations make it difficult to perform randomized controlled trials [2,3]. However, such involuntary treatments are indispensable in many clinical practice scenarios, and they are commonly used as strategies to treat patients exhibiting disruptive and violent behaviors [3-7].

The Mental Health Act in Japan was initially passed on May 1, 1950, and was originally called the Mental Hygiene Law. In 1988, the Mental Hygiene Law was revised and renamed the Mental Health Law. In 1995, the current version, the Mental Health and Welfare Law, came into force [8-10]. All psychiatrists practicing in Japan must abide by this law, which provides for the fundamental human rights of people with psychiatric problems.

The Mental Health and Welfare Law defines three types of admission: voluntary hospitalization, hospitalization for medical care and protection, and involuntary hospitalization ordered by a prefectural governor [11]. In Japan, the judicial process does not become involved in decision-making about involuntary hospitalizations. Instead, the Japanese government empowers designated physicians for mental health to be entrusted with safeguarding the rights of subjects with psychiatric conditions. Designated physicians also have the right and duty to initiate and terminate coercive measures such as seclusion and restraint.

In 1998, after the disclosure of human rights violations in some Japanese psychiatric hospitals and in response to pressing social demand, Asai et al. conducted a national survey about involuntary psychiatric treatments and published a detailed report and guidelines the following year [12]. Asai and his collaborators distributed survey sheets to 1,548 hospitals with psychiatric beds and received 1,090 responses (70.4 percent), suggesting an increasing interest in this topic. After this survey and elaborate analysis, official guidelines on restraint and seclusion were published by the Japanese Society of General Hospital Psychiatry's educational committee http://psy.umin.ac.jp/[13]. The issuance of these guidelines deepened clinical psychiatrists' awareness of behavioral restrictions and educated practitioners about the importance of these measures as potential therapeutic strategies in psychiatric emergencies. However, opportunities for studying psychiatric seclusion and restraint are limited when compared to opportunities to study pharmacotherapy or psychotherapy.

The aim of this survey was to learn Japanese psychiatrists' attitudes about emergency interventions for acute psychosis by focusing on involuntary treatments and exploring the possibility of minimizing psychiatric coercive measures.

Methods

Subjects

The subjects of this study were 183 young Japanese psychiatrists. Site investigators were recruited through the Japan Young Psychiatrists Organization's (JYPO; http://jypo.umin.jp/) listserv, and those site investigators in turn encouraged their colleagues to participate in the survey. We provided three options for answering the questionnaire: online, email, or conventional mail. The study authors mailed a questionnaire to site investigators at the collaborating institutes. The site investigators physically distributed the questionnaire to their colleagues or sent an email with the URL and login password for the online questionnaire. All subjects were requested to complete the questionnaire during the survey period, January 1 to February 28, 2009. The purpose of this study was clearly stated on the cover sheet of the questionnaire and answering the questionnaire was considered to be consent. All responders participated in this study without any incentive. Similarly, all authors and subjects involved in this study declared themselves free of any conflict of interest relating to the study.

Questionnaire Contents

The questionnaire consisted of a case vignette and questions in three categories: (1) the use of hospitalization; (2) the length of inpatient care, and (3) the use of seclusion and/or restraint [see Additional file 1]. After reading the case vignette, all respondents were asked to score the need for involuntary hospitalization, identify the type of admission, estimate the length of inpatient care, and the likelihood of prescribing seclusion and/or restraint.

The questionnaires were returned anonymously. However, respondents were asked to provide demographic information regarding their levels of psychiatric experience, the types of facilities in which they worked, the region in which they practice, and whether they were designated mental health physicians. The questionnaire is shown in the Appendix.

Statistical Analysis

Study results were expressed as mean ± SD. Statistical analysis was performed using SPSS 16.0J for Windows (SPSS Japan Inc., Tokyo, Japan). A student's t-test and ANOVA were applied, respectively, for the comparisons of two groups and three or more groups. The statistical significance was set at a p value of less than 0.05.

Results

A total of 183 young psychiatrists answered this study's questionnaire. We collected data from all seven regions in Japan, with relatively higher rates in Hokkaido/Tohoku and Kyushu. Because we used three different methods of data collection (online, email, or conventional mail), it was difficult to calculate a precise total response rate. The response rate for the email attachments and conventional mail was 93.3% (n = 112). However, several factors complicated the response rate calculation for the Internet data collection because some mailing lists used in this study contained a number of invalid addresses. Based on the estimated response rate reported by each site investigator, we estimated the total response rate at approximately 85%. Because of a defect in the questionnaire sheet as distributed during the earliest stage of this study, for 65 out of 183 respondents (35.5 percent) it was impossible to connect scores on a 9-point scale and the psychiatrists' length of clinical experience. The average length of psychiatric experience was 7.49 ± 5.6 (mean ± SD) years (n = 118). The rate of designated physicians was 50.8 percent. Designated mental health physicians had significantly greater clinical experience (11.30 ± 5.2 years, n = 60) as compared to non-designated psychiatrists (3.45 ± 2.2, n = 58). For the type of facility, 103 of the survey participants worked at university hospitals, 36 at general hospitals, and 34 at psychiatric hospitals, and the remaining 10 respondents worked at psychiatric clinics, academic schools, or public health facilities.

The study results were summarized in tables. Almost all respondents (98.9 percent) scored 7 or higher regarding the need for hospitalization, including 162 psychiatrists who scored 9 (88.5 percent) as shown in Table 1. Most respondents scored 7 or higher on a 9-point Likert scale regarding the likelihood of prescribing seclusion (8.43 ± 1.0), whereas the scores regarding prescribing restraint displayed a greater diversity (5.14 ± 2.5).

Table 1: The need for hospitalization, its form and length, and the likelihood of prescribing seclusion and/or restraint.

Necessity of hospitalization	**9 point scale (9 = strongly agree)**	
Overall (n = 183)	8.91 ± 0.3	
Designated physician for mental health (n = 60)	8.85 ± 0.5	p = 0.28
Non-designated physician (n = 58)	8.93 ± 0.3	
Form of admission	Out of 183 respondents	
Voluntary Hospitalization	0	
Medical Care and Protection	77 (42.1%)	
Ordered by Prefectural Governor	104 (56.8%)	
No answer	2 (1.1%)	
Estimated length of hospitalization	Weeks	
Overall (n = 183)	13.53 ± 6.4	
Designated physician for mental health (n = 60)	14.07 ± 7.3	p = 0.31
Non-designated physician (n = 58)	12.88 ± 5.0	
Likelihood of seclusion	9 point scale (9 = strongly agree)	
Overall (n = 182)	8.43 ± 1.0	
Designated physician for mental health (n = 59)	8.51 ± 0.9	p = 0.35
Non-designated physician (n = 58)	8.33 ± 1.2	
Likelihood of restraint	9 point scale (9 = strongly agree)	
Overall (n = 183)	5.14 ± 2.5	
Designated physician for mental health (n = 60)	4.98 ± 2.5	p = 0.37
Non-designated physician (n = 58)	5.40 ± 2.4	

Survey results are expressed with a mean ± SD. P values were calculated with a Student's t-test between the two subgroups. No statistically significant differences were found.

Regarding the likelihood of prescribing restraint, a two-group comparison between designated and non-designated physicians demonstrated no significant difference. However, psychiatrists working at general hospitals did score significantly higher (6.25 ± 2.5) than those who work at university hospitals (5.02 ± 2.3) or psychiatric hospitals (4.15 ± 2.6) as illustrated in Table 2.

We divided the survey respondents into two groups, based on scores regarding the likelihood of prescribing restraint: those psychiatrists who favored restraint (score 7-9) and those who were opposed (score 1-3). Those psychiatrists who favored the use of restraint were found to estimate significantly shorter periods of inpatient care (12.22 ± 4.0) than those professionals who opposed restraint (14.22 ± 7.4).

Discussion

Every psychiatrist must pay careful attention to avoid violating human rights when initiating coercive treatments such as seclusion and restraint. However, these interventions are indispensable in clinical psychiatry, and they are often used as strategies in the treatment of agitated patients.

The Mental Hygiene Law was intended to protect the fundamental human rights of people with mental illness and facilitate their rehabilitation within the community. Since enactment of the law in 1950, all psychiatric medical professionals in Japan have been bound to practice psychiatry with careful consideration to avoid infringing upon human rights. There have been certain calls from a humanitarian viewpoint for the abolition of seclusion and restraint. However, in acute psychiatry, these coercive measures can be useful therapeutic strategies to ensure the safety of psychiatric patients [3-7]. In Japan, judgment regarding the necessity for involuntary psychiatric admission is entrusted to designated mental health physicians. The judicial system never becomes involved in this decision-making process. In order to admit a patient for hospitalization to provide medical care and protection, a designated physician obtains written consent from that patient's guardian [11,14].

Article 29 of the Mental Health and Welfare Law states that if a prefectural governor recognizes that a person who has been examined is diagnosed as mentally disordered and is therefore likely to hurt himself/herself or others unless hospitalized for medical care and protection, the prefectural governor may admit the person to a mental hospital established by the national or prefectural government or a designated hospital. This form of forced hospitalization can be approved only when the person has been examined by at least two designated physicians and the examination results of each physician conclude that the person is mentally disordered and that he or she is likely to hurt himself/herself or others because of a mental disorder unless admitted to a hospital for medical care and protection.

In Japan, there is no uniform residency program in each medical specialty. Instead of standardized training programs, there is a two-tier psychiatric training system in Japan: (1) specialist certification by the Japanese Society of Psychiatry and Neurology; and (2) government designation. To become a designated mental health physician, applicants for designation must have clinical experience exceeding five years, including over three years in general

Table 2: Comparing the likelihood of prescribing restraint and the estimated hospitalization length.

Likelihood of Restraint	9 point scale (9 = strongly agree)	
Overall (n = 183)	5.14 ± 2.5	
Designated mental health physician (n = 60)	4.98 ± 2.5	p = 0.37[1]
Non-designated physician (n = 58)	5.40 ± 2.4	
University hospital (n = 103)	5.02 ± 2.3	
General hospital (n = 36)	6.25 ± 2.5	p = 0.03[2]
Psychiatric hospital (n = 34)	4.15 ± 2.6	p = 0.001[3]
Estimated length of hospitalization	weeks	
Agreed with restraint (score 7-9, n = 62)	12.22 ± 4.0	p = 0.049
Disagreed with restraint (score 1-3, n = 55)	14.22 ± 7.4	

Survey results are expressed with a mean ± SD. p values were calculated using Student's t-test between the two subgroups. Significant differences were found between those psychiatrists practicing in general hospitals and the two other types of hospitals. No significant variation was found between psychiatrists in university and psychiatric hospitals.
Significance of difference between:
[1] Designated mental health physician and Non-designated physician
[2] University hospital and general hospital
[3] General hospital and psychiatric hospital

psychiatry. Designated mental health physician candidates must take a three-day course of lectures and submit eight case reports of involuntary hospitalization in six categories: schizophrenia (three case reports including at least one case in which the patient was admitted by a prefectural gubernatorial order, which is the most coercive type of hospitalization), mood disorder, substance abuse, dementia, organic disorders, and child and adolescent mental health. Thus, the main purpose of this designation system is to thoroughly acquaint psychiatrists with the Mental Health Law and authorize psychiatrists to execute various involuntary interventions based on Japan's strict mental health regulations.

According to the results of the present study, the average score ranking the necessity of hospitalization was 8.91 ± 0.3 on the 9-point Likert scale, with 98.9 percent of respondents scoring a 7 or higher. With regard to the form of admission, opinions were nearly divided in half: 42.1 percent responded that hospitalization for medical care and protection would be most likely, whereas 56.8 percent said an involuntary hospitalization ordered by a prefectural governor would be a likely type of admission. In the case vignette used in this study, Mr. A. brandished a kitchen knife and threatened his neighbors. This behavior may be considered to satisfy the legal requirements for involuntary hospitalization. However, in real life situations, hospitalization for medical care and protection, a less coercive measure, is more commonly suggested. The polarization of the respondents' opinions on this point might be attributable to differences in their interpretations of the case vignette.

There was significant diversity among the respondents' estimations of hospitalization length, which ranged from four weeks (n = 4) to one year (n = 1). The majority of respondents suggested twelve weeks (n = 106), with an average of 13.53 ± 6.4 weeks. Two group comparisons between the designated mental health physicians and the non-designated physicians revealed no statistically significant difference between the two groups' estimations of hospitalization length. Further, no correlations were found between the estimated hospitalization length and the likelihood of prescribing restraint, nor were correlations discovered between the estimated hospitalization length and the length of physicians' psychiatric experience. However, the two group comparisons between psychiatrists who favored restraint and those who opposed it revealed that those practitioners who favored restraint suggested a significantly shorter hospitalization length than those who opposed restraint. We cannot provide a clear explanation for this result. The result might indicate that restraint is considered an outcome of treatments that target earlier improvement in the manifestation of psychiatric symptoms. Hoge et al. reported that most episodes of refusal to take antipsychotic medication by consumers ended with voluntary acceptance of treatment [15]. However, it takes time to persuade patients to take oral medication and often requires additional staff. To ensure minimum coerciveness in psychiatric practice, we need additional studies to explore those factors affecting psychiatrists' decisions about initiating coercive measures.

Psychiatrists in other countries may consider a three-month hospitalization to be somewhat excessively long. However, it is noteworthy that Japan has been criticized for its lengthy hospitalization periods for schizophrenic patients [11]. When considering this national mental health care backdrop, the three-month hospitalization suggested in this study certainly reflects the recent improvements in Japanese psychiatrists' awareness about shortening hospital stay durations. In the treatment case presented, the patient lives alone and has no prior history of psychotic episodes. Unfortunately, Japan still suffers from a lack of social resources enabling people with mental disorders to live within their communities. Further measures are needed to shorten the length of hospital stays.

For employing seclusion versus restraint, the score for the likelihood of prescribing seclusion showed a high concurrence rate among the respondents, with an average of 8.43 ± 1.0 on a 9-point scale. Alternatively, the score for the likelihood of prescribing restraint ranged from 1 to 9, with an average of 5.14 ± 2.5. In Japan, seclusion in a room with a certain amount of space and equipped with a bathroom is considered less restrictive than restraint. At a previously held international workshop on seclusion and restraint that we organized, we realized through discussions with psychiatrists from other countries that cultural backgrounds would influence psychiatrists' opinions about behavioral restrictions [16]. For instance, when the Czech Republic became a target of criticism because of their use of a cage bed--a bed surrounded by a metal cage used to restrain a patient--the Czechs explained that in the Czech Republic the use of a "net bed" was considered more humane than other restraint techniques, such as straps, isolation rooms, or even strong medication. It is important to understand that differences in psychiatric opinions may be due to differences between cultural backgrounds [17].

When comparing scores for estimated hospitalization lengths, according to the types of hospitals where physicians work, those who work at general hospitals suggested a significantly longer period than those who work at university hospitals or psychiatric hospitals. One reason for this result could be explained by the psychiatric departments in most general hospitals being understaffed while having a higher percentage of patients requiring restraint,

for example, people who are sent to the emergency room with an altered level of consciousness or delirium patients with comorbid physical conditions. Another reason could be that there are increasing numbers of patients with behavioral and psychological symptoms of dementia (BPSD) resulting from the rapid aging of the Japanese population. Yet another reason for expecting a longer hospitalization period at general hospitals might be the nurses' working environment. It has been reported that training nurses is effective in decreasing the number of behavioral restrictions at hospitals [18,19]. However, certain nursing system characteristics in the psychiatric wards of many general hospitals could be hindering this effect. For instance, nurses in general hospitals are routinely transferred to different wards after a certain period of time and therefore are likely to be less experienced, tending to resign sooner because of their workload.

As for limitations of this survey, the questionnaire was sent to the subjects with a brief description of an imaginary case rather than a real patient. The subjects of this study represent only a subset of psychiatrist in Japan. The latest data provided by the Japanese Ministry of Health, Labor and Welfare reports that the total number of psychiatrists was 12,474, accounting for 4.49% of all medical doctors in 2006 (on-line database of JMHLW; http://www.mhlw.go.jp/toukei/). The number of doctors under the age of 40 was 93,409 in 2006. Considering these data, we estimated the number of young psychiatrists as 4,194. Thus, the subjects of this study account for 4.36% of all young Japanese psychiatrists. Similarly, the number of designated physicians for mental health was 11,791 in 2006. Our sample included only 0.5% of those designated physicians, indicating limited representation. In regard to the 9-point scale used in this study, a 5 score indicates neither agreement nor disagreement on a 9-point Likert scale (with 9 being the highest possible score) and the significance of the deviation from the mean of 5 remains controversial. Therefore, it is difficult for us to draw firm conclusions.

Conclusion

In recent years, many studies have been conducted on psychiatric seclusion and restraint, especially in Europe [20-22]. It has been reported that some programs have succeeded in reducing restraint [23,24]. A previous study revealed that experiencing coercion during admission negatively affected patients' attitudes toward treatment and adherence to medication [25]. We believe that psychiatrists early in their careers should consider how to minimize the use of behavioral restrictions. It is feasible that early training determines the subsequent clinical custom of each psychiatrist. Going forth into clinical duties with this in mind will no doubt shorten the hours of seclusion and restraint for current and future patients.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The members of Coercive Treatment in Psychiatry Study Group of Japan Young Psychiatrists Organization (MT, KS, KU, DF, YZ, NH, HT, NY, SS) designed the study protocol and collected data in collaboration with site investigators (TK, WN, YW, TS, SK). All authors had full access to the data. MT performed the statistical analysis and drafted the manuscript. All authors have read and approved the final manuscript.

Additional material

Additional file 1

Questionnaire. The questionnaire with case vignette used in this study.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1752-4458-3-20-S1.DOC]

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References

1. WHO: *Mental health legislation & human rights (Mental health policy and service guidance package)* Geneva: World Health Organization; 2003.
2. Muralidharan S, Fenton M: **Containment strategies for people with serious mental illness.** *Cochrane Database Syst Rev* 2006, **3**:CD002084.
3. Sailas E, Fenton M: **Seclusion and restraint for people with serious mental illnesses.** *Cochrane Database Syst Rev* 2000:CD001163.
4. Sailas E, Wahlbeck K: **Restraint and seclusion in psychiatric inpatient wards.** *Curr Opin Psychiatry* 2005, **18(5)**:555-559.
5. Cotton NS: **The developmental-clinical rationale for the use of seclusion in the psychiatric treatment of children.** *Am J Orthopsychiatry* 1989, **59(3)**:442-450.
6. Nelstrop L, Chandler-Oatts J, Bingley W, Bleetman T, Corr F, Cronin-Davis J, Fraher DM, Hardy P, Jones S, Gournay K, *et al.*: **A systematic review of the safety and effectiveness of restraint and seclusion as interventions for the short-term management of violence in adult psychiatric inpatient settings and emergency departments.** *Worldviews Evid Based Nurs* 2006, **3(1)**:8-18.
7. Fisher WA: **Restraint and seclusion: a review of the literature.** *Am J Psychiatry* 1994, **151(11)**:1584-1591.
8. Asai K: **From mental health law to mental health and welfare law.** *Psychiatry Clin Neurosci* 1998, **52(Suppl)**:S247-249.
9. Koizumi K, Harris P: **Mental health care in Japan.** *Hosp Community Psychiatry* 1992, **43(11)**:1100-1103.
10. Salzberg SM: **Japan's new Mental Health Law: more light shed on dark places?** *Int J Law Psychiatry* 1991, **14(3)**:137-168.
11. Tsuchiya KJ, Takei N: **Focus on psychiatry in Japan.** *Br J Psychiatry* 2004, **184**:88-92.
12. Asai K: **A study on minimizing behavioral restrictions in psychiatry:Behavioral restrictions on subjects with psychiatric disorders and protection of human rights [in Japanese].** In *A report of the study supported by Health Sciences Research Grant (1999-2000)* Chiba, Japan; 2000.
13. Hatta K: *A guideline for restraint and seclusion [in Japanese]* Tokyo: Seiwa Shoten; 2007.

14. Shiraishi H: **Reform of "hogosha" system and psychiatric practice in Japan.** *Jpn J Psychiatry Neurol* 1994, **48(Suppl)**:117-124.
15. Hoge SK, Appelbaum PS, Lawlor T, Beck JC, Litman R, Greer A, Gutheil TG, Kaplan E: **A prospective, multicenter study of patients' refusal of antipsychotic medication.** *Arch Gen Psychiatry* 1990, **47(10)**:949-956.
16. Kato T, Baba T, Sugiura K, Tateno M, Balhara Y, Sharifi V, Tseng H, Zin NM, Kabir M, Rahman J, *et al.*: **Asian Young Psychiatrists' International Workshop in the 104th Annual Meeting of the Japanese Society of Psychiatry and Neurology.** *WPA e-bulletin Third quarter (Jul-Sep)* 2008:42-49.
17. Holt E: **Rest and restraint.** *Lancet* 2004, **364(9437)**:829-830.
18. Needham I, Abderhalden C, Halfens RJ, Fischer JE, Dassen T: **Non-somatic effects of patient aggression on nurses: a systematic review.** *J Adv Nurs* 2005, **49(3)**:283-296.
19. Ito H, Eisen SV, Sederer LI, Yamada O, Tachimori H: **Factors affecting psychiatric nurses' intention to leave their current job.** *Psychiatr Serv* 2001, **52(2)**:232-234.
20. Martin V, Bernhardsgrutter R, Goebel R, Steinert T: **The use of mechanical restraint and seclusion in patients with schizophrenia: a comparison of the practice in Germany and Switzerland.** *Clin Pract Epidemol Ment Health* 2007, **3**:1.
21. Steinert T, Bergbauer G, Schmid P, Gebhardt RP: **Seclusion and restraint in patients with schizophrenia: clinical and biographical correlates.** *J Nerv Ment Dis* 2007, **195(6)**:492-496.
22. Kallert TW, Glockner M, Onchev G, Raboch J, Karastergiou A, Solomon Z, Magliano L, Dembinskas A, Kiejna A, Nawka P, *et al.*: **The EUNOMIA project on coercion in psychiatry: study design and preliminary data.** *World Psychiatry* 2005, **4(3)**:168-172.
23. Hellerstein DJ, Staub AB, Lequesne E: **Decreasing the use of restraint and seclusion among psychiatric inpatients.** *J Psychiatr Pract* 2007, **13(5)**:308-317.
24. Gaskin CJ, Elsom SJ, Happell B: **Interventions for reducing the use of seclusion in psychiatric facilities: review of the literature.** *Br J Psychiatry* 2007, **191**:298-303.
25. Day JC, Bentall RP, Roberts C, Randall F, Rogers A, Cattell D, Healy D, Rae P, Power C: **Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals.** *Arch Gen Psychiatry* 2005, **62(7)**:717-724.

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Regional dopamine synthesis in patients with schizophrenia using L-[β-^{11}C]DOPA PET

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ABSTRACT

The dopamine hypothesis has been the most widely known theory concerning schizophrenia. However, the exact mechanism including presynaptic dopaminergic activity and its relationship with symptom severity still remains to be revealed. We measured presynaptic dopamine synthesis using positron emission tomography (PET) with L-[β-^{11}C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as k_i values, were obtained using a graphical method, and the occipital cortex was used as reference region. Regions of interest were placed on the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). We found significantly higher k_i values in patients than in controls in the left caudate nucleus, but not in the other regions. The k_i values in the thalamus exhibited a significant positive correlation with the PANSS total scores. Furthermore, a significant positive correlation was observed between the PANSS positive subscale scores and k_i values in the right temporal cortex. Patients with schizophrenia showed higher dopamine synthesis in the left caudate nucleus, and dopaminergic transmission in the thalamus and right temporal cortex might be implicated in the expression of symptoms in schizophrenia.

1. Introduction

Positron emission tomography (PET) has allowed us to investigate the dopamine hypothesis in living human brain. Since there is no ideal animal model of schizophrenia, PET investigation is still the most useful method for investigating neurotransmission in patients. As for postsynaptic dopaminergic receptors, several studies have investigated striatal (Farde et al., 1990; Nordström et al., 1995; Wong et al., 1986) and extrastriatal (Suhara et al., 2002; Yasuno et al., 2004) D_2 receptor (D_2R) binding by the use of PET. Although studies investigating D_2R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D_2R binding have repeatedly reported its reduction in the anterior cingulate cortex (Suhara et al., 2002) and the thalamus in schizophrenia (Talvik et al., 2003; Yasuno et al., 2004). Regarding intrasynaptic function, striatal dopamine release was reported to be enhanced in schizophrenia (Breier et al., 1997; Laruelle et al., 1996). On the other hand, many studies did not find any change in dopamine transporter binding in the striatum of schizophrenia (Laakso et al., 2000;

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Laruelle et al., 2000; Schmitt et al., 2005; Yang et al., 2004). These findings suggest that patients with schizophrenia may have elevated presynaptic dopamine synthesis, and investigations on presynaptic dopaminergic function in extrastriatal regions might be critical for providing an understanding of the pathophysiology of schizophrenia.

Radiolabeled L-DOPA, a precursor of dopamine, has been used to investigate presynaptic dopamine synthesis. L-DOPA is transported through the blood–brain barrier (BBB), taken up by presynaptic monoaminergic neurons, and metabolized to dopamine by aromatic amino acid decarboxylase (AADC). Previous studies on the dopamine synthesis of schizophrenia used 6-[^{18}F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashef et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[β-^{11}C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[^{18}F]fluoro-L-DOPA, which is widely used in schizophrenia research, indicated elevated dopamine synthesis (Hietala et al., 1995, 1999; Lindström et al., 1999; McGowan et al., 2004; Reith et al., 1994), elevated dopamine turnover (Kumakura et al., 2007), only higher variability (Dao-Castellana et al., 1997), and even reduced synthesis (Elkashef et al., 2000) in the striatum.

The 3-O-methyl metabolite of L-DOPA crossing the BBB can reportedly cause an error in quantification of the dopamine synthesis rate (Dhawan et al., 1996; Melega et al., 1990; Wahl et al., 1994). However, 3-O-methylation of L-[β-^{11}C]DOPA does not take place readily and rapidly when compared with 6-[^{18}F]fluoro-L-DOPA (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Recently, we evaluated the accuracy of quantitative analyses of L-[β-^{11}C]DOPA PET studies (Ito et al., 2006). In the current study, we investigated regional dopamine synthesis and its relationship with the severity of positive and negative symptoms in patients with schizophrenia using L-[β-^{11}C]DOPA.

2. Methods

2.1. Participants

Fourteen (8 males and 6 females) drug-naïve and 4 (2 males and 2 females) 3-month drug-free patients (35.6± 7.4 years, mean±SD) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia or schizophreniform disorder were recruited from the outpatient units of university hospitals, their affiliated psychiatric hospitals, and a mental clinic. On the day of the PET study, the diagnosis was re-evaluated by 3 experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The severity of psychotic symptoms was also evaluated by the same 3 psychiatrists with the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Igarashi et al., 1998). Each interview was conducted by 2 of 3 authors (S.N., F.Y., M.O.) and one other psychiatrist. Patients with schizophreniform disorder (2 males and 2 females) at the time of the PET study were followed up for at least 6 months from onset, confirming that they eventually met the criteria of schizophrenia. Twenty (10 males and 10 females) healthy volunteers (35.1±9.5 years) were recruited as controls through public notices. All the subjects were examined by physicians to obtain data concerning their educational background as well as current and past medical problems, and family history by unstructured interview and a general questionnaire. Handedness was assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971). The control subjects were matched with the patients for age, gender, education, and handedness. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. The demographic characteristics of all participants are shown in Table 1. Exclusion criteria of patients and controls were as follows: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse including alcohol; (3) previous episodes of mood disorder. One patient was excluded because of a large cyst in the cerebellum (data not shown).

After giving explanation of the study, written informed consent was obtained from all patients and control subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET study

All the participants were instructed to fast for 4 h before PET scan in order to avoid the influence of the plasma concentration of neutral amino acid (NAA) on the L-[β-^{11}C]DOPA uptake rate. A PET scanner (ECAT EXACT HR , CTI-Siemens, Knoxville, TN), providing 63 planes with an axial field of view of 15.5-cm, was used. A head fixation device (Fixster, Stockholm Sweden) was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Data acquisition was performed in 3-dimensional mode with the interplane septa retracted. A bolus of 331.5 to 401.8 MBq (373.0±14.1 MBq, mean±SD) of L-[β-^{11}C]DOPA with specific radioactivities (9.9–156.4 GBq/μmol) was injected intravenously via the antecubital vein and flushed rapidly with 20 mL of saline. Dynamic scans were performed for 64 min immediately after the injection. The scanning sequence consisted of seven 1-min frames, five 2-min frames, four 3-min frames, and seven 5-min frames. All emission scan data were reconstructed with a Hanning filter with a cutoff frequency of 0.4 (final in-plane resolution: 7.5 mm full width at half maximum).

Table 1
Demographic and clinical characteristics of patients with schizophrenia and normal controls

	Controls (n=20)	Patients (n=18)
Gender, M/F	10/10	10/8
Age, y, mean±SD	35.1±9.5	35.6±7.4
Range	20–55	20–52
Medication, no. naïve (M/F)/free (M/F)		14 (8/6)/4 (2/2)
Handedness, no. right/left	20/0	18/0
Education, y, mean (range)	15.1 (12–9)	14.1 (9–16)
No. of smokers (M/F)	4 (4/0)	6 (4/2)
Duration of illness, mo, mean (range)		26.4 (1–120)
PANSS		
Whole score		
Mean±SD		79.2±21.4
Range		46–124
Subscales		
Positive (mean±SD)		22.6±7.3
Negative (mean±SD)		17.1±6.5
General psycho (mean±SD)		39.6±11.0

Table 2
k_i values of each ROI in patients with schizophrenia and normal controls

Region	L/R	Controls	Patients	ANCOVA#	
		(n=20)	(n=18)	F	p
Parahippocampus	L	4.54±1.13	4.91±1.45	0.704	0.407
	R	4.76±1.11	4.47±1.29	0.528	0.472
Temporal cortex	L	1.92±0.99	1.98±0.81	0.041	0.842
	R	1.86±0.83	1.92±0.87	0.037	0.849
Prefrontal cortex	L	1.31±0.73	1.22±0.64	0.324	0.573
	R	1.35±0.73	1.35±0.57	0	1.000
Thalamus	L	3.55±1.60	3.19±1.72	0.549	0.463
	R	3.11±1.45	3.09±1.54	0.001	0.970
Putamen	L	15.52±2.04	15.76±2.14	0.139	0.711
	R	15.39±2.31	14.90±3.01	0.329	0.570
Caudate	L	12.89±2.68	14.66±2.38	4.409	0.043*
	R	13.71±2.74	13.59±2.09	0.026	0.872
Anterior cingulate	L	2.74±1.33	3.05±1.50	0.445	0.509
	R	3.24±1.73	3.00±1.13	0.288	0.595

Dopamine synthesis rates, expressed as $k_i \times 1000$, were presented as mean± standard deviation.
#: Analysis of covariance with age as covariate (df=1, 35).
L indicates left and R indicates right. The symbol * represents $p<0.05$.

2.3. Magnetic resonance images

For each participant, a structure magnetic resonance (MR) image was obtained. All MR imaging studies were performed with a 1.5-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, TE: 9.2 ms; repetition time, TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256×256; slice thickness: 1 mm).

2.4. Data analysis

All MR images were coregistered to the PET summation images of all frames using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROIs) were drawn on the coregistered MR images, referring to the human brain atlas (Mai et al., 1997), and then transferred to the PET images. ROIs were defined for the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. The ROIs were set on both left and right sides of the brain and those values were independently evaluated. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

The overall uptake rate constant k_i of L-[β-^{11}C]DOPA, which indicates the net dopamine synthesis rate, was determined for each ROI by the graphical plot analysis method developed by Gjedde and Patlak (Gjedde, 1982; Ito et al., 2006; Patlak and Blasberg, 1985). k_i values can be estimated by simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F_{t>t^*}$$

where C_i is the total radioactivity concentration in a brain region that can be measured by PET, C_i' is the total radioactivity concentration in the reference brain region with no irreversible compartments, and t^* is the equilibrium time of the compartment for unchanged radioligand in the brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after the time t^*, yields a straight line with the slope k_i and intercept F. In the present study, the occipital cortex was used as reference region (Ito et al., 2006). A range of equilibrium time t^* of 31.5 to 61.5 min was used.

ROI analyses were independently performed by 3 researchers who were blinded to the diagnoses. The intraclass correlation coefficient across all ROIs was 0.976 (McGraw and Wong, 1996), considered as excellent. In order to reduce variance, the k_i values by one researcher that most frequently showed medium values among those obtained by the 3 researchers were used for the following analyses.

2.5. Statistical analysis

Demographic variables were compared by independent sample t-test or chi-square test. Differences in the k_i values for each of the 7 × 2 brain regions between patients and controls were evaluated by one-way univariate analyses of covariance with age as a covariate, since an effect of age on k_i values has been reported (Ota et al., 2006). Pearson's correlation coefficients were calculated between the PANSS scores and k_i values. A significance level of $p<0.05$ (two-tailed) was used both in the comparison analyses between groups and in the correlation analyses.

3. Results

3.1. Demographic data

The demographic data of schizophrenia patients and controls are shown in Table 1. There were no significant differences between patients and controls in terms of age, gender, education, handedness, and the injected dose and

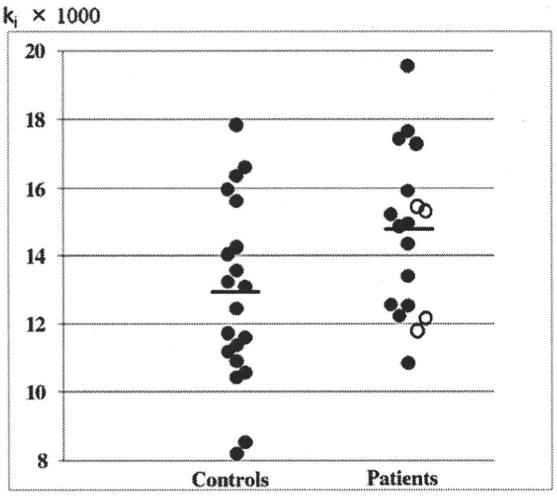

Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those of drug-free patients.

Table 3
Correlations between k_i values of each ROI and PANSS scores in schizophrenia

Region	L/R	Total scores		Positive symptoms		Negative symptoms		General symptoms	
		r	p	r	p	r	p	r	p
Parahippocampus	L	−0.003	0.992	0.045	0.859	0.080	0.752	−0.083	0.745
	R	0.284	0.253	0.288	0.246	0.197	0.434	0.245	0.328
Temporal cortex	L	−0.088	0.728	0.133	0.598	−0.049	0.848	−0.232	0.355
	R	0.465	0.052	0.603	0.008*	0.242	0.334	0.361	0.141
Prefrontal cortex	L	0.380	0.120	0.288	0.246	0.339	0.168	0.346	0.160
	R	0.407	0.094	0.302	0.082	0.457	0.057	0.320	0.196
Thalamus	L	0.620	0.006*	0.490	0.039*	0.504	0.033*	0.589	0.010*
	R	0.470	0.049*	0.378	0.122	0.492	0.038*	0.372	0.129
Putamen	L	0.247	0.323	0.177	0.482	0.342	0.165	0.160	0.525
	R	0.359	0.143	0.327	0.186	0.407	0.094	0.240	0.338
Caudate	L	0.287	0.323	0.294	0.236	0.319	0.197	0.174	0.490
	R	−0.183	0.468	−0.223	0.375	0.021	0.935	−0.220	0.380
Anterior cingulate	L	−0.270	0.120	0.202	0.421	−0.418	0.085	−0.412	0.089
	R	0.355	0.149	0.421	0.082	0.303	0.222	0.231	0.357

L indicates left and R indicates right.
The symbol * represents $p<0.05$.

specific radioactivity of L-[β-^{11}C]DOPA. The duration of illness and the PANSS scores are also shown in Table 1.

3.2. Regional L-[β-^{11}C]DOPA uptake in schizophrenia and control subjects

Univariate analysis of covariance revealed no significant interaction between group and age in any of the regions, and a significant group difference in k_i values only for the left caudate between normal controls and schizophrenia patients was observed ($df=1, 35$, $F=4.409$, $p=0.043$; Table 2 and Fig. 1). In addition, no significant difference was observed in the k_i values between antipsychotic drug-naïve and drug-free patients in any of the regions.

Furthermore, there was no significant correlation between the k_i values in any ROIs and the duration of illness in patients.

3.3. Severity of positive and negative symptoms and L-[β-^{11}C] DOPA uptake

Relationships between k_i values in each ROI and the PANSS total and subscale scores are presented in Table 3. Significant positive correlations were observed between the k_i values in both sides of the thalamus and the PANSS total scores (left: $r=0.620$, $p=0.006$; right: $r=0.470$, $p=0.049$). With regard to PANSS subscales, the k_i values in the left thalamus correlated positively with the PANSS positive, negative, and general symptom subscales, and those in the right thalamus correlated with the PANSS negative symptoms. In addition, a positive correlation was observed in the right temporal cortex between the k_i values and the PANSS positive subscale scores ($r=0.603$, $p=0.008$).

4. Discussion

In the present study, we found increased dopamine synthesis in the left caudate nucleus in patients with schizophrenia compared to normal controls. In addition, we observed a significant correlation between regional dopamine synthesis in the thalamus as well as in the right temporal cortex and symptom severity in patients.

Most of the previous studies with 6-[^{18}F]fluoro-L-DOPA have reported elevated dopamine synthesis mainly in the striatum of patients with schizophrenia (Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994), whereas decreased (Elkashef et al., 2000) or only greater variability (Dao-Castellana et al., 1997) have also been reported in this region. There are some plausible explanations for these inconsistent results. First, the participants with schizophrenia in these studies were not homogeneous. For example, one study investigated heterogeneous patients with psychosis (Reith et al., 1994), while the other studies included patients with schizoaffective disorder (Hietala et al., 1995, 1999). Furthermore, schizophrenia patients on antipsychotic medication participated in two of the PET studies (Elkashef et al., 2000; McGowan et al., 2004). Interestingly, a study on only unmedicated schizophrenia patients showed only greater variability in k_i values compared with normal controls (Dao-Castellana et al., 1997). Second, the differences between 6-[^{18}F]fluoro-L-DOPA and L-[β-^{11}C]DOPA in terms of 3-O-methyl metabolite of L-DOPA crossing the BBB might also result in such inconsistency (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Kumakura et al. reported a method to reduce this problem with metabolites and demonstrated that catabolism and elimination of 6-[^{18}F]fluoro-L-DOPA was elevated nearly 2-fold in the striatum in 8 patients with schizophrenia as compared to that in 15 age-matched control subjects. They concluded that not only the synthesis but also the turnover of radiolabeled dopamine was increased in patients with schizophrenia (Kumakura et al., 2007).

Lindström et al. (1999) investigated unmedicated schizophrenia patients using L-[β-^{11}C]DOPA and found increased dopamine synthesis in the striatum and medial prefrontal cortex, while we observed elevated dopamine synthesis only in the left caudate. As for differences between the two studies, however, the patients in the study of Lindström et al. had relatively more severe psychotic symptoms (Clinical Global Impression ≥4) than our patients. In addition, our patients were mostly outpatients, and thus, such a difference in the demographic of patients might be responsible for the difference in results. In addition, the caudate nucleus might be more important than the putamen in the pathophysiology

of schizophrenia because the caudate has extensive interconnections from the limbic and cortical areas, which play crucial roles in the regulation of cognition and emotion compared to the putamen (Parent, 1990). Further, lateralization to the left of the caudate is consistent with the reports by Hietala et al. (1995, 1999).

With regard to the relationships with symptoms, in our patients, presynaptic dopamine synthesis in the thalamus was positively correlated with overall symptom severity, although that in the right thalamus was correlated only with PANSS negative scores, besides the PANSS total scores; in addition, dopamine synthesis in the right temporal cortex was positively correlated with positive symptoms. The thalamus has been repeatedly reported to be engaged in the pathophysiology of schizophrenia (Clinton and Meador-Woodruff, 2004; Takahashi et al., 2006). Previous neuroimaging studies have shown altered thalamic perfusion and metabolism (Andreasen et al., 1997; Buchsbaum et al., 1996; Clark et al., 2001; Hazlett et al., 1999, 2004; Kim et al., 2000; Mitelman et al., 2005; Resnick et al., 1988) and decreased dopamine D_2 receptor availability in the thalamus in patients with schizophrenia (Buchsbaum et al., 2006; Talvik et al., 2003, 2006; Yasuno et al., 2004). The thalamus is reported to have a pivotal role in the processing and integrating of sensory information related to emotional and cognitive functions (Clinton and Meador-Woodruff, 2004), and it has also been suggested to have sensory gating function (Carlsson et al., 2000; Takahashi et al., 2006). Further, elevated dopamine transmission in the thalamus was reported to disrupt sensory gating function (Young et al., 1995). Impaired gating function could contribute to both positive and negative symptoms by the inability to automatically "gate out" much redundant and unessential information, leading to irrelevant thought and fragmentation of mind and behavior in schizophrenia (Braff et al., 1999). Additionally, one study with 6-[^{18}F]fluoro-L-DOPA examined before and after 5 weeks of haloperidol treatment for schizophrenia demonstrated that the thalamus was the only structure in which the change of dopamine synthesis was related to improvement in negative symptoms (Gründer et al., 2003). Thus, dopaminergic regulation in the thalamus might be associated with positive and negative symptoms in schizophrenia. However, the contribution of different roles of each side of the thalamus to diverse symptom dimensions remains unclear.

In terms of the correlation between dopamine synthesis in the right temporal cortex and the PANSS scale, our data suggested that higher dopamine synthesis in the right temporal cortex might be associated with the expression of positive symptoms in patients with schizophrenia. Previous functional MRI studies have demonstrated the involvement of the right temporal cortex in some of the positive symptoms such as auditory hallucination (Shergill et al., 2000; Woodruff et al., 1997) and formal thought disorder (Kircher et al., 2002) in schizophrenia. On the other hand, although previous PET (Buchsbaum et al., 2006) and SPECT (Tuppurainen et al., 2003) studies have suggested decreased dopamine D_2R binding in the right temporal cortex, no significant correlation was found between the binding and positive symptoms. Furthermore, no study has demonstrated the relationship between presynaptic dopamine synthesis in the right temporal cortex and positive symptoms.

There are several limitations in the present study. First, smoking is regarded as a confounding factor in the estimation of k_i values (Salokangas et al., 2000), and some of our participants were smokers, although the smoking rate of the patients was only slightly higher than that of the normal controls (33% for patients and 20% for controls). Second, our patients consisted of both males and females, although we selected age- and gender-matched control subjects. Laakso et al. (2002) indicated gender differences in striatal dopamine synthesis with the use of 6-[^{18}F]fluoro-L-DOPA PET. However, we did not find such differences in our subjects (data not shown). Nonetheless, since gender differences have been suggested in schizophrenia (Salem and Kring, 1998), this issue should be addressed in future studies. Finally, although our sample size is hitherto the largest among reported studies on dopamine synthesis in schizophrenia, the current study may still not have enough power. Our results of both comparison and correlation analyses were significant only when uncorrected for multiple comparisons, and the failure to observe significant correlations with symptoms in other regions might be due to a type II error. Therefore, further investigations using still larger samples are required.

5. Conclusion

We measured the dopamine synthesis rate in patients with schizophrenia and normal control subjects by using PET with L-[β-^{11}C]DOPA. Patients had higher dopamine synthesis in the left caudate nucleus than controls, which was in line with the results of most previous studies that indicated an increase in dopamine synthesis in the striatum. Moreover, correlation analyses between k_i values and symptoms suggested that dopamine synthesis in the thalamus and right temporal cortex might be implicated in the pathophysiology of schizophrenia. There is little evidence concerning extrastriatal presynaptic dopaminergic functions of schizophrenia in vivo. Further studies are required to better understand the presynaptic dopaminergic functions of schizophrenia.

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Contributors

S. Nozaki, F. Yasuno, A. Takano, and T. Suhara designed the study and wrote the protocol. S. Nozaki, M. Kato, F. Yasuno, M. Ota, A. Otsuka, and Y. Okubo recruited the patients and made psychiatric evaluations. S. Nozaki, H. Takano, M. Okumura, R. Arakawa, R. Matsumoto, and Y. Fujimura participated in the data analysis. S. Nozaki wrote the first draft of the manuscript. S. Nozaki, M. Kato, H. Takano, H. Takahashi, H. Ito, H. Kashima and T. Suhara had discussions and corrected the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors have no conflict of interest.

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