

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 μ M DMT reversibly inhibited I_{Na} by $29 \pm 3\%$ ($n = 7$ WT myocytes), whereas I_{Na} was reduced by only $7 \pm 2\%$ ($n = 7$ 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 potentially inhibited by haloperidol (28). Although haloperidol is thought to act in part through the dopamine D_2 receptor system, it is also a potent sigma-1 receptor agonist [sigma-1 inhibition constant (K_i) = 3 nM (29); sigma-2 K_i = 54 nM (29)] when inhibiting voltage-gated ion channels (5, 25). Haloperidol reduces brain concentrations of DMT (8) and DMT inhibits haloperidol binding in brain tissue more robustly than the dopamine agonist apomorphine (8). On the basis of these findings, which were discovered before sigma receptor identification, DMT has been hypothesized to act through an unknown "hallucinogen" receptor (8). We confirmed results (28) that intraperitoneal (ip) administration of DMT (2 mg per kilogram of body weight) 2 hours after pargyline (75 mg/kg, ip) injection induced hypermobility in WT mice (7025 ± 524.1 cm, $n = 12$ WT mice) in an open-field assay. Identical drug treatments in sigma-1 receptor KO mice had no hypermobility action (2328 ± 322.9 cm, $n = 12$ KO mice, $P < 0.0001$; Fig. 4, A and B). This result is particularly important to our understanding of sigma-1 receptor biological function because the KO mice are viable and fertile (27). The sigma-1 receptor dependence of DMT-induced hypermobility parallels that induced by the sigma-1 receptor ligand (+)-SKF10047 in WT but not in KO mice (27). As a positive control, methamphetamine, which is thought to act through catecholaminergic systems, induced hypermobility in both WT and KO mice (3 mg/kg, ip, $n = 6$ mice; Fig. 4, B and C) with a reduced onset rate compared with that seen for DMT (Fig. 4, A and C). This indicates that behavioral actions of DMT depend on the sigma-1 receptor, which may provide an alternative research area for psychiatric disorders that have not been linked to dopamine or N -methyl-D-aspartate systems.

The binding, biochemical, physiological, and behavioral studies reported here all support the hypothesis that DMT acts as a ligand for the sigma-1 receptor. On the basis of our binding results and the sigma-1 receptor pharmacophore, endogenous trace amines and their N -methyl and N,N -dimethyl derivatives are likely to serve as endogenous sigma receptor regulators. Moreover, DMT, the only known mammalian N,N -dimethylated trace amine, can activate the sigma-1 receptor to modulate Na^+ channels. The recent discovery that the sigma-1 receptor functions as a molecular chaperone (30) may be

relevant, because sigma-1 receptors, which are observed in the endoplasmic reticulum, associate with plasma membrane Kv 1.4 channels (22) and may serve as a molecular chaperone for ion channels. Furthermore, the behavioral effect of DMT may be due to activation or inhibition of sigma-1 receptor chaperone activity instead of, or in addition to, DMT/sigma-1 receptor modulation of ion channels. These studies thus suggest that this natural hallucinogen could exert its action by binding to sigma-1 receptors, which are abundant in the brain (1, 27). This discovery may also extend to N,N -dimethylated neurotransmitters such as the psychoactive serotonin derivative N,N -dimethylserotonin (bufotenine), which has been found at elevated concentrations in the urine of schizophrenic patients (10). The finding that DMT and sigma-1 receptors act as a ligand-receptor pair provides a long-awaited connection that will enable researchers to elucidate the biological functions of both of these molecules.

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31. We thank the Corinna Burger laboratory for use of their mouse behavior equipment, and A. Paul and T. Mavlyutov for providing [125 I]IAF and [125 I]-IACoc, respectively. Supported by the Molecular and Cellular Pharmacology (MCP) Graduate Program training grant from NIH T32 GM08688 and by the NIH Ruth L. Kirschstein National Research Service Award (NRSA) (F31 DA022932) from the National Institute on Drug Abuse (to D.F.). This work was funded by NIH grants R01 MH065503 (to A.E.R.) and NS30016 (to M.B.J.).

Supporting Online Material

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

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

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

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

Envy is one of the seven biblical sins, the Shakespearean "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 neuroimag-

ing studies (21, 22). Each participant was presented with a scenario in which the protagonist (oneself) and three other target persons appeared. Materials were employed from an initial survey to validate our expected results (23). Before the fMRI scans, we asked the participants to read and understand the scenario thoroughly and to imagine the protagonist of the scenario as themselves. In study one, we aimed to determine the level of envy in terms of whether possessions of the target person were superior or not and whether domains of comparison were self-relevant or not. In short, for male participants, the protagonist of the scenario was male and average in terms of possessions such as ability, quality, and social status. Male student A shared similar attributes with the protagonist. He possessed superior quality and ability, and the domains of comparison were important and relevant to the protagonist [superior and high relevance (SpHi)]. Female student B had different attributes and background from the protagonist. She also possessed superior quality and ability, but the domains of comparison were neither important nor relevant to the protagonist [superior and low relevance (SpLo)]. Female student C had different attributes and background from the protagonist. She possessed mediocre quality and ability, and the domains of comparison were neither important nor relevant to the protagonist [average and low relevance (AvLo)]. The scenario for male participants and profiles of the persons are shown in the

appendix in (23). The profiles of the three target persons and comparison domains are summarized in table S1, and a schematic depiction of the stimuli and design is shown in fig. S1. We performed event-related fMRI analysis with statistical parametric mapping 2 to examine activations in response to SpHi, SpLo, and AvLo. In study two, successive misfortunes happened to student A (SpHi) and student C (AvLo) in the scenario examining reaction in response to misfortunes happening to others. A list of misfortunes is provided in table S1, and a schematic depiction of the stimuli and design is shown in fig. S2. We analyzed neural responses to misfortunes on SpHi (MisSpHi) and AvLo (MisAvLo). After the scans, the participants rated each event presented in study one in terms of how much envy they felt for the three students (i.e., 1 = no envy, 6 = extremely envious). Similarly, the participants also reported the intensity of their pleasure (*schadenfreude*) (1 = no pleasure, 6 = extremely pleasant) in response to misfortunes happening to students A and C in study two. That is, they gave one envy score per domain per student in study one and one *schadenfreude* score per misfortune per student in study two.

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



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

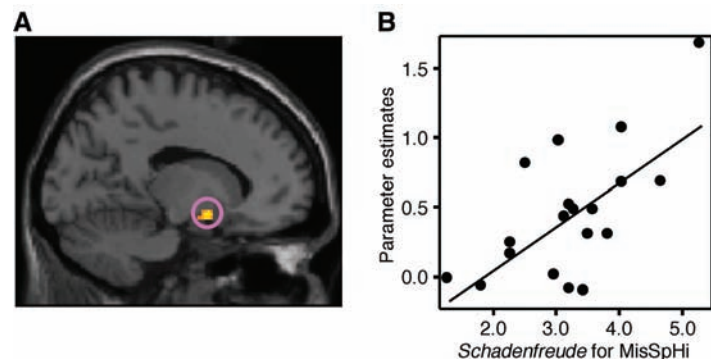


Fig. 2. Correlation between self-rating of *schadenfreude* and ventral striatum activation across participants. (A) Image showing correlation between mean rating of *schadenfreude* for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. (B) Plots and regression line of correlation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

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

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

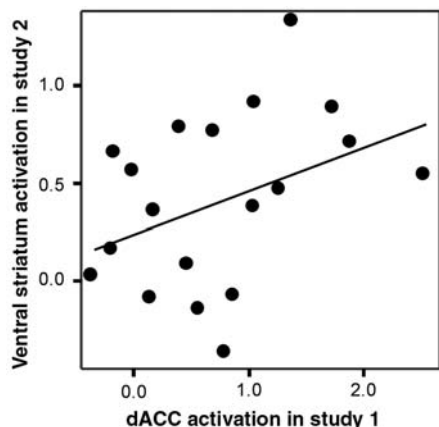


Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (-2 , 10 , 52). The y axis indicates the parameter estimates of the ventral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

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

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

We are usually motivated to maintain a positive self-concept (16), and we feel discomfort when our self-concept is threatened by others who outperform ourselves in a self-relevant domain. Considering the role of dACC in conflict-monitoring (19), the association between envy and dACC activation suggests that envy is a condition in which information recognized by social comparison conflicts with positive self-concept. Experiencing discomfort motivates us to reduce it. Discomfort arising from others outperforming us in our cherished domains can be resolved by reducing the relevance of the domain to us or changing relative performance (16). Students in our scenario might change their major or club at the university and, ultimately, their goals in life. Alternatively, they might make an effort to improve their own performance or possession. On the contrary, they might wish that the other lacks advantages, or they may even obstruct the advantaged student (with malice). Similarly, from an economic perspective, envy has productive and destructive effects on economic growth. It motivates the members in organizations to enhance their own performances or to sabotage their opponents' performances (24). When misfortune occurs to an advantaged person and contributes to narrowing the gap of relative performance in an important domain, discomfort or pain is reduced, and a pleasant feeling is induced. This pleasure at another's misfortune is correspondent to the activation of the ventral striatum and the medial orbitofrontal cortex (25, 26). The striatum has also been implicated in altruistic punishment (27) and observing an unfair person receiving pain (28). Stronger dACC activation induced by the

most envied student in study one predicted stronger ventral striatum activation when misfortunes occurred to the student in study two. This means that people who tend to have higher pain or conflict are more likely to have a strong pleasant feeling once they are relieved from this pain. Thus, our findings propose a neurocognitive mechanism of a psychologically rewarding reaction, schadenfreude, and its relation to envy. At the same time, ventral striatum activation without receiving an actual reward indicates that we did not evaluate objects solely by their absolute value but that social comparison plays a substantial role in evaluation (29).

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

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Materials and Methods

SOM Text

Figs. S1 to S4

Table S1

8 September 2008; accepted 10 December 2008

10.1126/science.1165604