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分担研究報告書

スポーツ・運動の統合失調症の認知機能・高次脳機能障害に対する効果に関する研究

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研究要旨

スポーツおよび運動が統合失調症の認知機能に与える影響ないしは効果を検討するためには、まず、その基礎的研究として、統合失調症例における随意運動、すなわち意図的運動の特徴を抽出することが重要であると思われる。昨年度の研究では、統合失調症の随意運動障害と認知機能の変化との関係を検討する第一歩として、統合失調症において異常が認められるとされる、意志作用感(sense of agency)ないしは自他帰属性に関して、健常例における計算論シミュレーション実験を行い、sense of agency という概念を用いて、行動学的な実験が可能であることを示した。本年度は、独自の agency 判断課題を作成し、統合失調症の臨床型によって sense of agency の異常パターンがどのように異なるかを検討した。妄想型統合失調症では over-attribution、残遺型で under-attribution、解体型では confusional pattern が示され、臨床型によって異なった sense of agency の障害パターンが明らかにされた。この結果は、様々な現われをする統合失調症の自我障害の形成機構を随意運動障害という側面から検討する上で興味深い結果である。

A．研究目的

統合失調症の一級症状でみられるような自我障害は、統合失調症に極めて特異的かつ本質的な症状であると考えられており、認知機能障害研究のターゲットとして重要である。近年、自己意識に関する神経科学が進められつつあり、特に統合失調症の自我障害との関連で注目されてきているのが、「 sense of agency （意志作用感・自己主体感）」に関する研究である。 sense of agency とは、自己が行為や思考の作用主体（ agent ）であるという感覚、すなわち自己の身体運動や外界で生じる事象を自己によって制御できるという主観的体験のことである。

過去のsense of agency課題の一つは、随意的行為と外的事象との因果連関における物理的時間を操作し、それに応じたagencyに関する主観的体験の変化について問うというexplicitな手法で、多くのsense of agency課題では、この方法をとっている。具体的には、コンピューターを用いて、被験者の操作（ key press, joy stick など）と画面上の反応に時間バイアス（ delay ）をプログラムしておき、被験者に自己が agent であると感じるかどうかについて問うものである。

いま一つは、随意的行為とその結果生じてくる外的事象において、時間体験そのものを問う implicit な手法である。例えば、自己の行為とそれに引き続いて起きる外的事象との‘時間的関連付け効果（Binding Effect）’に関する Haggard らの研究がある。用いる課題はLibet課題で、被験者がボタンを押して250msec の time lag の後に音が鳴るようにしておき、被験者が主観的にはどれくらいの time lag として体験しているかについて問うものである。

我々は、これまでのタスクに比べて施行が容易で、臨床的に重症な症例をも対象とし得るような新たな sense of agency task を考案し、臨床型によって、どのような異常パターンを示すかについて検討した。

B．研究方法

対象は、 DSM-IV によって診断された慢性期の統合失調症患者30名。うち、妄想型12名、残遺型12名、解体型 6 名。コントロール群として、双極性障害 8 名。健常群22名。各グループの詳細は **Table 1** に示す。本研究は、桜ケ丘記念病院の倫理委員会に承認され、検査はインフォームドコンセントを得た上で施行した。

TABLE 1

	Paranoid type (N=12)	Residual type (N=12)	Disorganized type (N=5)	Bipolar disorder in remission (N=8)	Normal controls (N=22)
Age	39.8(14.5)	36.0(8.2)	42.8(9.5)	34.8(9.5)	33.9(9.7)
Gender	M 7, F 5	M 6, F 6	M 4, F 1	M 4, F 4	M 10, F 12
Education(years)	13.3(2.1)	14.1(2.5)	13.2(1.8)	13.4(1.8)	16.5(1.3)
Outpatient/Inpatient	10/2	10/2	4/1	7/1	—
Duration of illness(years)	12.8(12.1)	10.5(6.7)	23.0(7.2)	14.6(8.2)	—
Neuroleptic dosage (HP-mg)	12.1(11.5)	15.7(15.5)	33.2(17.5)	5.76(6.60)	—
GAF	53.0(15.4)	45.6(17.6)	27.2(3.0)	84.0(10.5)	—
PANSS (total score)	79.1(12.2)	85.8(17.0)	123.4(5.9)	—	—
Positive symptoms	21.4(5.7)	18.2(4.7)	23.4(2.6)	—	—
Negative symptoms	16.0(2.9)	24.4(4.3)	34.4(2.4)	—	—
General psychopathology	41.7(6.1)	43.3(9.8)	65.6(2.3)	—	—

Means(SD)

実験は、14インチのパソコンモニターを用いて施行。各試行は、5mm四方の四角形がスクリーンの下方から上方へ一定のスピード（22m /sec）で進む。被験者は、音を合図にボタンを押すように指示され、そのボタン押しに連動して四角形のpieceが35mm上方へジャンプするようにプログラムしてある（**Figure 1**）。その際、ボタン押しとジャンプの間に0～1000msec（100msec毎）の delay をランダムに導入し **(Figure 2a)**、一試行毎に“piece を自分で動かした感じがするか否か?”あるいは“自分がコントロールしている感じがするか否か？”とagency判断を行い、YES-NOの回答を求められる。また、 sham 条件として、ボタン押しにではなく、音に連動して反応する条件も設定（delay: －100ms, 0ms, 100ms）（**Figure 2b**）。各条件10 試行で合計140 試行を行う。

グループごとに各条件の中央値（median）を計算し、各条件ごとに比較する。統計解析はMann-Whitney's U検定による。

FIGURE 1

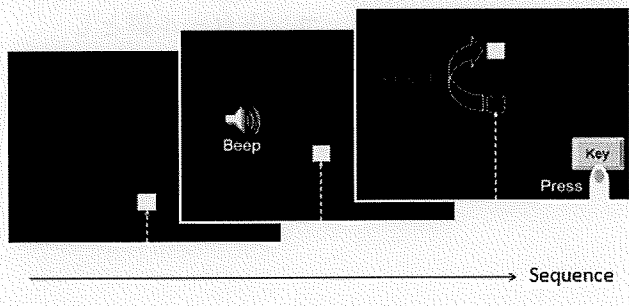
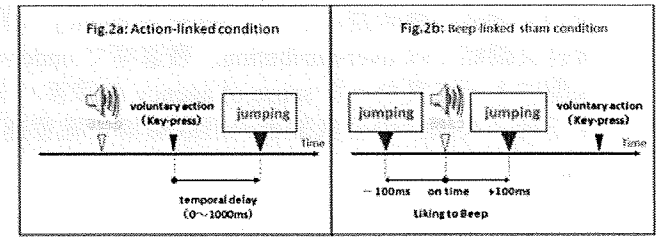


FIGURE 2



C．研究結果

健常群と比べ、妄想型では delay が長くても自己を agent と判断、すなわち self-agency の増強（over-attribution）、残遺型では delay が少しでもあると自己が agent ではないと判断、すなわち self-agency の低下（under-attribution）が見られた。解体型では self-agency が一定せず over-attribution と nder-attribution とが併存しており、agency判断が混乱していた (confusional pattern)（**Figure 3**）。このように、統合失調症では、あらゆる臨床型において sense of agencyの異常が認められるが、そのパターンは質的に異なるものであった。双極性障害では健常パターンを示した。 sham 条件については、健常群では、YES判断はみられないが、統合失調症ではYES判断がみられた（**Figure 3**）。

D．E．考察と結論

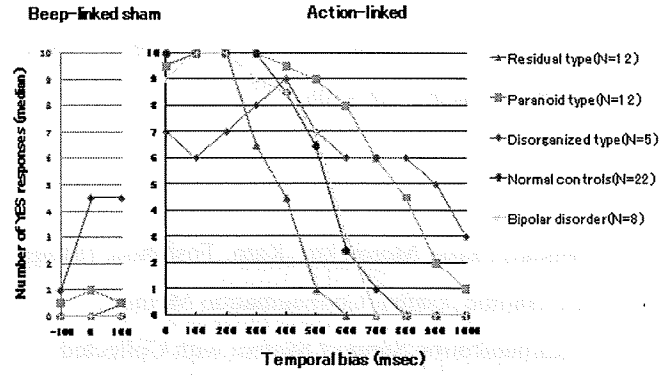
統合失調症における sense of agency は臨床型によって異なるパターンを呈することを示した。妄想型においては、先行研究と同様に over-attribution を呈した。一方、残遺型統合失調症では、under-attribution を示した。これまでの報告では、統合失調症において実験的に under-attribution をとらえた研究はない。今回の研究により、自我障害のシミュレーションモデル上で予想された、under-attribution がはじめて実験上確認された。本研究では検査が平易なた

め、臨床的に重度の残遺型を対象とすることができたことによるものと考える。

先に紹介したHaggard らの 'Binding Effect' に関する研究によれば、統合失調症では、意図的・能動的に行為したときにのみ、健常人よりも強く binding effect が現れるということであった。これは、主体の態度、すなわち能動性の発動様態が規定条件となって、統合失調症の自我障害 dynamic に変化するということであり、自我障害はstaticなものではないということである。臨床型によるagency異常の差異は、主体の能動性に関連するstrength of intentionの機能状態の差異に因るのではないかと考えられる。すなわち、残遺型ではstrength of intentionが低下しているために外界の事象に対してagencyが低下するが、妄想型ではstrength of intentionが保たれていおるために、'Binding Effect' と同様に外界の事象と自己とが結びつくためagencyが強まるのではないかと考えられる。自我障害は基本障害から直接的に導かれるものではなく、能動性の発動状態という非特異的要因が症状形成的に作用しているものと考えられる。

臨床的観点から言えば、あらゆる臨床型においてagencyの異常が認められることから、本テストが、統合失調症の客観的な診断マーカーとなりうるのではないかと考えている。

FIGURE 3



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F．健康危険情報

特に問題なかった。

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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.

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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

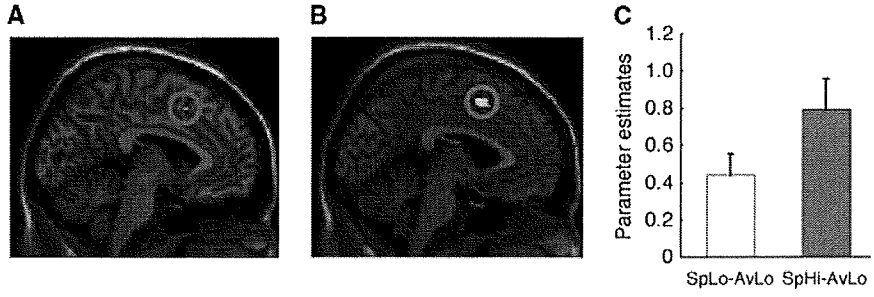

Fig. 1. Brain activation in dACC was modulated by relevance of comparison domain. Brain activations in response to **(A)** the SpLo minus AvLo condition and **(B)** the SpHi minus AvLo condition. **(C)** Mean for parameter estimates at the peak of dACC activation for SpHi-AvLo contrast (red) was greater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

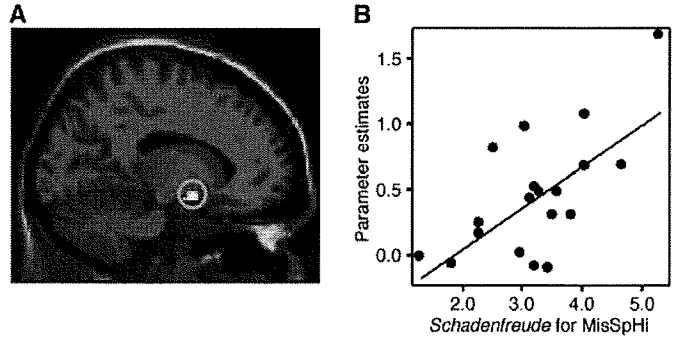

Fig. 2. Correlation between self-rating of schadenfreude and ventral striatum activation across participants. **(A)** Image showing correlation between mean rating of schadenfreude for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. **(B)** Plots and regression line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

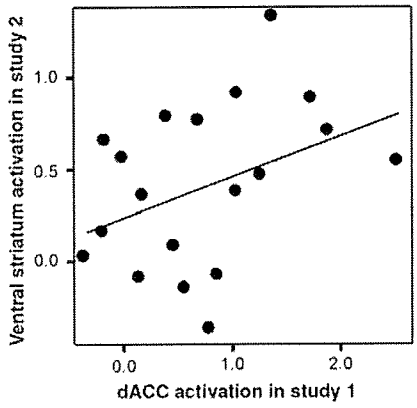

Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (–2, 10, 52). The y axis indicates the parameter estimates of the ventral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

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Supporting Online Material

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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.

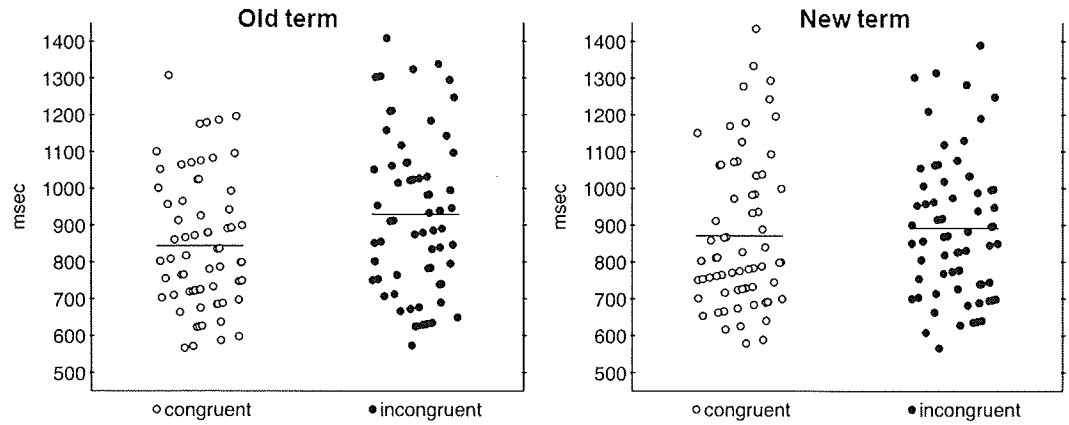

Fig. 1. Average response latency for CC and IC in old- and new-term versions of IAT. White dots indicate CC and black dots indicate IC. The bars represent the mean response latency of each condition. ANOVA revealed that response latencies were significantly longer for old term than for new term in IC, 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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