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Functional Deficits in the Extrastriate Body Area During Observation of Sports-Related Actions in Schizophrenia

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Exercise and sports are increasingly being implemented in the management of schizophrenia. The process of action perception is as important as that of motor execution for learning and acquiring new skills. Recent studies have suggested that body-selective extrastriate body area (EBA) in the posterior temporal-occipital cortex is involved not only in static visual perception of body parts but also in the planning, imagination, and execution of actions. However, functional abnormality of the EBA in schizophrenia has yet to be investigated. Using functional magnetic resonance imaging (fMRI) with a task designed to activate the EBA by sports-related actions, we aimed to elucidate functional abnormality of the EBA during observation of sports-related actions in patients with schizophrenia. Twelve schizophrenia patients and 12 age-sex–matched control participants participated in the study. Using sports-related motions as visual stimuli, we examined brain activations during observation of context-congruent actions relative to context-incongruent actions by fMRI. Compared with controls, the patients with schizophrenia demonstrated diminished activation in the EBA during observation of sports-related context-congruent actions. Furthermore, the EBA activation in patients was negatively correlated with the severity of negative and general psychopathology symptoms measured by the Positive and Negative Syndrome Scale. Dysfunction of the EBA might reflect a difficulty in representing dynamic aspects of human actions and possibly lead to impairments of simulation, learning, and execution of actions in schizophrenia.

Key words: body/extrastriate body area/schizophrenia/sports/exercise/fMRI

Introduction

With the introduction of atypical antipsychotics, awareness of these comorbid metabolic disturbances in schizophrenia has become considerably increased among many health care professionals and patients.[1] For the management of comorbid metabolic disturbances, exercise is one of the most acknowledged interventions.[2] At the same time, exercise and sports have been recognized as having a positive impact on the treatment and rehabilitation of schizophrenia.[3] However, individuals living with schizophrenia are less physically active than the general population.[4,5] Moreover, they generally show psychomotor poverty and clumsiness[6] and have an impairment of motor skill learning,[7,8] which have been suggested to be linked to a dysfunctional motor execution system including the striatum-frontal-cerebellum.[9,10]

It is widely documented in psychological and neurocognitive studies that the systems that mediate action perception, imitation, planning, and execution overlap and interact with each other.[11,12] These studies have supported the view that when we observe others' actions, observed action is automatically simulated and matched with internal motor representation and could even be imitated unconsciously (Chameleon effect).[12,13] These externally triggered motor representations are then used to understand, learn, and reproduce the observed behavior.[14] Therefore, for learning and acquiring new skills, the process of action perception is as important as that of motor execution.

Passive viewing of biological motions has been known to activate the superior temporal sulcus (STS),[15] and the STS has been suggested to have a more extended function in social cognition such as detecting intention of

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others.[16,17] Kim et al[18] reported that schizophrenia patients were impaired in the perception of biological motion, and they predicted that impaired biological motion processing arises from functional deficit in the STS. Although the STS is a central node of processing biological motion, passive viewing of biological motion has consistently activated the posterior temporal-occipital cortex including the body-selective extrastriate body area (EBA)[19] in close proximity to the STS.[20] Originally, the EBA was identified as an area that responds selectively to static human bodies and body parts.[19] In biological motion tasks, low-level visual stimuli such as random moving dots have been used as control task, which make it difficult to clarify whether the EBA is only involved in body-sensitive early visual processing or is participant as a part of a system for inferring the action and intention of others like the STS. However, recent studies have suggested an extended role for the EBA, involving not only static visual perception of body parts but also the planning, imagination, and execution of actions.[21,22] In addition, we have shown that sports-related context-congruent actions produced greater activation in the EBA, along with the STS, than context-incongruent actions.[23] Compared with frontal or limbic areas, the posterior temporal-occipital or temporal-parietal cortex has received relatively little attention in the field of schizophrenia research,[24] and functional abnormality of the EBA in schizophrenia has yet to be investigated. We hypothesized that patients with schizophrenia would show diminished activation in the EBA, along with the STS, in response to sports-related context-congruent actions.

Methods

Participants Twelve patients with schizophrenia (6 men and 6 women, mean age: 31.8 ± 7.2 [SD] years) were studied. Diagnoses were based on the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* Axis I Disorders. All patients were attending the day hospital unit of Asai Hospital. Exclusion criteria were current or past substance abuse and a history of alcohol-related problems, mood disorder, or organic brain disease. The mean illness duration was 9.8 ± 6.9 years. All patients received antipsychotics (mean chlorpromazine equivalent daily dosage = 641.6 ± 471.2 mg).[25,26] Clinical symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.[27] Mean total scores of PANSS and subscale (positive scale, negative scale, and general psychopathology scale) were 69.8 ± 13.6, 14.3 ± 4.0, 19.7 ± 4.7, and 35.8 ± 6.4, respectively. The ratings were reviewed by trained senior psychiatrists, H.T. and T.S., after the patient interviews, and disagreements were resolved by consensus; consensus ratings were used in this study. Twelve age-sex–matched normal controls (6 men and 6 women, mean age 29.4 ± 4.5 years) were recruited from the surrounding community. The candidates were carefully screened, and standardized interviews were conducted by H.T. and T.S.. They did not meet criteria for any psychiatric disorders. None of the controls were taking alcohol or medication at the time, nor did they have a history of psychiatric disorder, significant physical illness, neurological disorder, or alcohol or drug dependence. All subjects were right-handed, and they all underwent a magnetic resonance imaging (MRI) to rule out cerebral anatomic abnormalities. All subjects had achieved an educational level of high school or higher. All of them had the experience of playing basketball in elementary school or junior high school, but they had little opportunity, if any, to play basketball thereafter. After complete explanation of the study, written informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Asai Hospital.

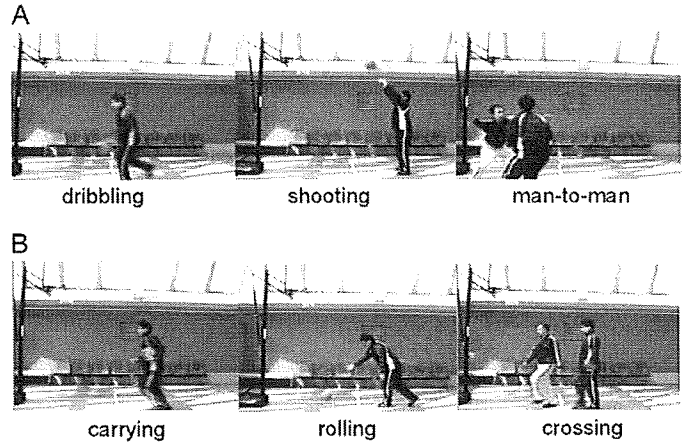

Fig. 1. Sample of Still Frames From Video Clips. A, Basketball-related motions; B, basketball-unrelated motions.

Materials

We employed the same visual stimuli as in the previous report where healthy volunteers were studied. The stimuli were designed to activate the EBA by sports-related actions.[23] Two types of video clips were provided (basketball-related motions [BRM] and basketball-unrelated motions [BUM]). Examples of the video clips are shown in figure 1. BRM consisted of 3 types of scenes (player shooting a free throw, player dribbling, 2 players performing man-to-man defense/offense). BUM also consisted of 3 types of scenes (player rolling a basketball, player carrying a basketball, and one person crossing in front of another without interaction). In order to make BRM and BUM as similar as possible, all players in the video clips performed in front of a basket hoop on a basketball court, and the number of persons, objects, motion direction, and speed were matched, ie, rolling a basketball, carrying a basketball, and crossing in front

of another without interaction corresponded to shooting a free throw, dribbling, and man-to-man defense, respectively. The video clips were projected via computer onto a screen mounted on a head coil. The subjects were instructed to pay attention to the video clips and to press a selection button with the right index finger when they watched the free throw scene and the basketball-rolling scene, indicating that they had paid attention to them. The experimental design consisted of 5 blocks for each of the 2 conditions (BRM and BUM) interleaved with 20-second rest periods. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In the BRM and BUM 24-second blocks, 3 scenes were presented twice for 4 seconds each.

Image Acquisition

Images were acquired with a 1.5-T Signa system (General Electric, Milwaukee, WI). Functional images of 115 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level–dependent contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; echo time (TE), 50 ms; repetition time (TR), 4 sec; matrix, 64 × 64; field of view, 24 × 24 cm). High-resolution, T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices; 3D Spoiled-Grass sequence; slice thickness, 1.5 mm; TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; field of view, 25 × 25 cm).

Analysis of Functional Imaging Data

Data analysis was performed with SPM02 (Wellcome Department of Cognitive Neurology, London, UK). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the Montreal Neurological Institute template. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (full width at half maximum of 8 mm). Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of the t statistic were calculated on a voxel-by-voxel basis.

To examine possible group differences in response to BUM (baseline), we conducted a 2-sample t test of BUM contrast. To assess the specific condition effect, we used the contrasts of BRM minus BUM. A random-effects model was implemented for group analysis. A 1-sample t test was applied to determine group activation for the contrasts of BRM minus BUM. Between-group comparison of BRM minus BUM contrast was performed with a 2-sample t test. We used SPM's small volume correction to correct for multiple testing in regions about which we had a priori hypotheses. These a priori volumes of interest (VOIs) included the EBA (inferior temporal cortex) and STS (superior temporal cortex). VOIs were defined by standardized VOI templates implemented in brain atlas software.[28] Significant differences surviving this correction at $P < .05$ were determined as were activations outside regions of interest surviving a threshold of $P < .001$, uncorrected, with an extent threshold of 10 contiguous voxels.

We conducted regression analyses to demonstrate a link between regional brain activities with the patients' demographics. Using the demographic data (age, duration of illness, chlorpromazine equivalent daily dosage, and PANSS scores) for each subject as covariates, regression analyses with the BRM minus BUM contrasts and the covariates were performed at the second level. The same threshold as used in the between-group comparison was applied. To confine the regions where significant group differences were observed, we created masks of group differences of the BRM minus BUM contrast from the 2-sample t test (threshold at $P < .05$, uncorrected), and these masks were applied inclusively. Using the effect sizes, representing the percent signal changes, of the BRM minus BUM contrasts at the peak coordinates uncovered in the regression analyses, we plotted the functional MRI (fMRI) signal changes and PANSS scores.

Results

Behavioral Data

All patients and controls paid attention to the video clips and pressed the button appropriately (accuracy was virtually 100%).

fMRI Results

In the control group, BRM minus BUM condition produced activations in the bilateral posterior temporal-occipital cortex including the bilateral EBA ($x = 58$, $y = -60$, $z = 2$; $t = 4.86$), middle temporal ($x = 54$, $y = -66$, $z = -12$; $t = 8.38$), right STS ($x = 56$, $y = -22$, $z = -2$; $t = 6.58$), bilateral premotor cortex ($x = -48$, $y = -4$, $z = 40$; $t = 4.94$), and bilateral inferior parietal lobules ($x = -34$, $y = -50$, $z = 54$; $t = 7.25$) (coordinates and t score refer to the peak of each brain region). In the patient group, BRM minus BUM condition produced activations in the left lingual gyrus ($x = -6$, $y = 92$, $z = 0$; $t = 6.52$), right prefrontal cortex ($x = 36$, $y = 52$, $z = 14$; $t = 5.66$), and right premotor cortex ($x = 36$, $y = -2$, $z = 54$; $t = 4.52$).

A 2-sample t test revealed no significant differences (threshold at $P < .001$, uncorrected) in the activations by BUM between controls and patients. Group comparison of the BRM minus BUM contrast showed that patients demonstrated significantly less activation in the bilateral EBA, bilateral parahippocampal gyrus, right STS, right temporal pole, right lingual gyrus, and globus

Table 1. Regions showing diminished activation in response to BRM-BUM condition in 12 patients with schizophrenia compared with 12 controls

Brain regions	R/L	MNI coordinates			BA	*t* value	voxels
		x	*y*	*z*			
EBA (MTG)*	L	−40	−60	−4	37	5.37	106
EBA (MTG)*	R	52	−68	6	37	5.08	74
STS (STG)*	R	54	−22	0	21, 22	6.61	100
Temporal pole (STG)	R	40	10	−28	38	4.04	27
Parahippocampal gyrus	R	26	−26	−20	35	5.92	111
Parahippocampal gyrus	R	18	−38	−4	30	5.12	25
Parahippocampal gyrus	L	−28	−44	−6	19, 37	4.08	48
Lingual gyrus	R	6	−92	−10	17	4.28	21
Globus pallidus	R	16	−10	−2		4.12	21

Coordinates and *t* value refer to the peak of each brain region. MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right; MTG, middle temporal gyrus; STG, superior temporal gyrus BRM, basketball-related motions; BOM, basketball-unrelated motions; EBA, extrastriate body area; STS, superior temporal sulcus. All values, $P < .001$, uncorrected. $^*P < .05$, corrected for multiple comparisons across a small volume of interest.

pallidus (table 1 and figure 2). The activations in a priori regions (EBA and STS) survived a threshold of $P < .05$ corrected for multiple comparisons across a small VOI. No significantly greater activation was identified in patients in the group comparison of the BRM minus BUM contrast.

Regression analysis revealed negative linear correlations between the negative scale score of PANSS and the degree of activation in the left EBA ($x = -58$, $y = -58$, $z = -6$; $t = 7.01$) in BRM minus BUM contrast (figure 3). Scores of the general psychopathology scale were also negatively correlated with the degree of activation in the left EBA ($x = -58$, $y = -56$, $z = -6$; $t = 5.81$) (figure 3). These correlations in a priori regions (EBA) survived a threshold of $P < .05$ corrected for multiple comparisons across a small VOI. There was no correlation between the positive scale score and regional brain activation. Regression analysis revealed that none of age, duration of illness, or chlorpromazine equivalent daily dosage had a relation with regional brain activation.

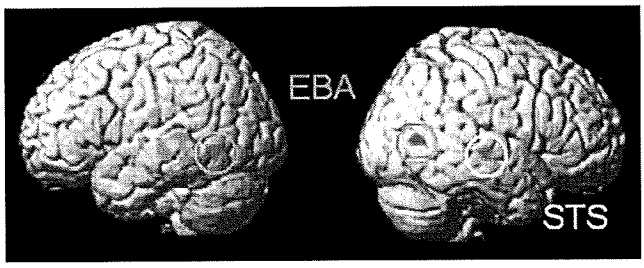

Fig. 2. Images Showing the Brain Area of Diminished Activations in Response to Basketball-Related Motions (BRM) Relative to Basketball-Unrelated Motions (BUM) Condition in 12 Patients With Schizophrenia Compared With 12 Normal Controls. Diminished activations in the bilateral extrastriate body area (EBA),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

Discussion

This study demonstrated that patients with schizophrenia showed diminished brain activations during observation of context-congruent actions in the EBA, along with the STS. The coordinates of the EBA were in good agreement with the previous literature (reviewed in Arzy et al[29]). The lesser activation of the STS in the patients was fairly predicted because previous psychological study has shown the impairment of biological motion perception in schizophrenia, which has been thought to be attributable to dysfunction of the STS.[18] The STS is located at a convergence zone for multimodal signals including limbic information,[30] and it has been suggested to be involved not only in the perception of biological motion but also in a more extended function of social cognition such as understating others' intention.[16,17] Dysfunctional STS might contribute to a difficulty in understanding intentional actions and behavior of agents in schizophrenia.[31]

The novel finding in this study was that the patients showed diminished EBA activation in response to context-congruent actions despite the fact that the patients comprehended explicit information of body movement (and basketball rules) similar to controls. This implies that the patients might not have processed implicit information carried by body movements as much as controls, but it is very difficult to quantify such implicit information and complex EBA function in a limited MRI environment and in a limited time period. Interestingly, PANSS score, instead of performance during fMRI scans, was directly linked to EBA activation in patients. That is, the less EBA activation was, the more severe the symptoms (negative and general psychopathology) in the patients were. The EBA was first identified as an area that responds selectively to static human bodies.[19] Recent studies have suggested that the EBA is also directly involved in representing the dynamic aspects of human

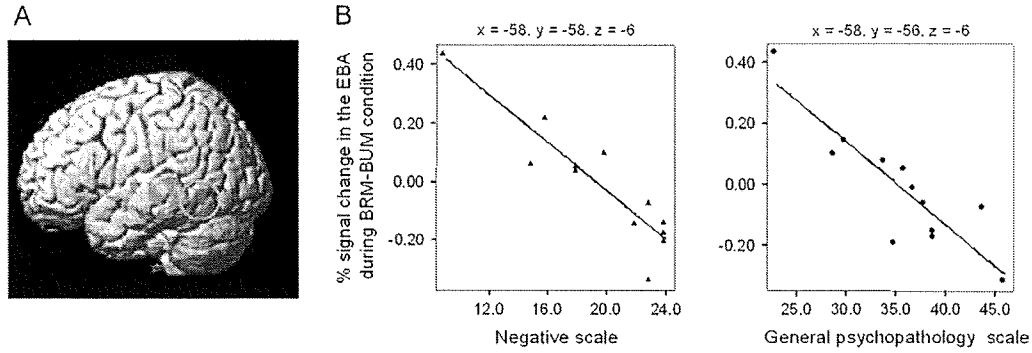

Fig. 3. Negative Correlations Between Positive and Negative Syndrome Scale (PANSS) Scores and the Degree of Activation in the Extrastriate Body area (EBA). A, Images showing negative correlation between negative scale scores and the degree of activation in the left EBA in basketball-related motions-basketball-unrelated motions (BRM-BUM) contrast. Scores of general psychopathology scale were also negatively correlated with the degree of activation in the left EBA in BRM-BUM contrast, yielding images identical to A. B, Plots and regression lines of negative correlations between PANSS scores and the degree of activation in the left EBA. The degrees of activations in the EBA were negatively correlated with the scores of negative scale ($r = -0.91$, $df = 10$; $P < .001$) and general psychopathology scale ($r = -0.88$, $df = 10$; $P < .001$).

motions as part of a system for inferring the intention of others.[32] Jackson et al[22] reported that, compared with observation of actions, EBA activation was enhanced during imitation. Furthermore, the motivation to act has been shown to modulate EBA activity.[33] These studies proposed an extended role for the EBA, involving the planning, execution, and imagination of actions. Our previous report that using the current task in healthy volunteers was in favor of this view,[23] suggesting that the EBA might contribute to the understanding of actions and intention of others through the mechanism of observed action being automatically represented and simulated.[14,32]

Empirical studies have shown that schizophrenia patients have difficulty in representing motor actions internally.[34,35] The diminished EBA activation in patients suggests that internal representation of the dynamic aspects of human motions is impaired. Motor representation is associated with understanding and rehearsing observed behavior.[14] In fact, recent studies demonstrated that motor representation is highly involved in skill learning and motor rehabilitation.[36,37] Consequently, the deficit in the EBA in schizophrenia could lead to difficulties in learning and reproducing new skills in addition to impairment in understanding others' actions.

The present study has several limitations. First, we examined only patients with chronic schizophrenia with long-term antipsychotic medication because our primary interest was the possible role of sports participation/observation in the management of chronic schizophrenia and comorbid metabolic disturbances partly due to antipsychotic medication. Medication possibly affects neural activation, but regression analysis revealed that chlorpromazine equivalent daily dosage has no relation with regional brain activation, and expression of dopamine D2 receptors in the posterior temporal-occipital cortex is extremely low.[38] Second, our task was not a behaviorally/cognitively demanding task leading to lack of dispersion in behavioral data (100% accuracy for both control and patient groups). Using a behaviorally/cognitively demanding task would require us to include only patients with psychiatric symptoms and cognitive impairments mild enough to undergo the imaging procedure and comply with the demanding task. However, the target patients of rehabilitation and management of comorbid metabolic disturbances in a day hospital have considerable behavioral and cognitive disturbances, which make it difficult to obtain reliable self-reported data of complex and subtle functions. Therefore, we employed the current task, aiming to examine patients with chronic schizophrenia in a real-world setting. From these limitations, it must be emphasized that any generalization of our findings to patients with first episode or nondeficit patients needs to be approached with caution.

In conclusion, chronic schizophrenia patients demonstrated diminished activation in the EBA in response to sports-related actions. Dysfunction of the EBA might reflect impairment of representation of dynamic aspects of human actions and might lead to impairments in simulation, learning, and execution of actions in schizophrenia. Furthermore, these impairments might lead to difficulty in understanding others' actions, interpersonal communication, body awareness, and overall physical activity manifested as negative symptoms and general psychopathology symptoms. The results of this study seem to have some important clinical implications for the management of chronic schizophrenia and merit further investigation in terms of the role of sports participation/observation in the rehabilitation for chronic schizophrenia and their effects on EBA function.

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Behavioral/Systems/Cognitive

Contribution of Dopamine D1 and D2 Receptors to Amygdala Activity in Human

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Several animal studies have demonstrated functional roles of dopamine (DA) D1 and D2 receptors in amygdala activity. However, the contribution of DA D1 and D2 receptors to amygdala response induced by affective stimuli in human is unknown. To investigate the contribution of DA receptor subtypes to amygdala reactivity in human, we conducted a multimodal *in vivo* neuroimaging study in which DA D1 and D2 receptor bindings in the amygdala were measured with positron emission tomography (PET), and amygdala response induced by fearful faces was assessed by functional magnetic resonance imaging (fMRI) in healthy volunteers. We used multimodality voxelwise correlation analysis between fMRI signal and DA receptor binding measured by PET. DA D1 binding in the amygdala was positively correlated with amygdala signal change in response to fearful faces, but DA D2 binding in the amygdala was not related to amygdala signal change. DA D1 receptors might play a major role in enhancing amygdala response when sensory inputs are affective.

Introduction

The amygdala plays a central role in processing affective stimuli, and in particular, threatening stimuli in the brain (LeDoux, 2000). The amygdala receives a moderate innervation of dopaminergic fibers (Asan, 1998), and both dopamine (DA) D1 and D2 receptors are expressed in this region (Ito et al., 2008), although the latter exhibit lower expression (Scibilia et al., 1992). DA release in the amygdala is increased in response to stress (Inglis and Moghaddam, 1999). It has been shown in animal studies that DA potentiates the response of the amygdala by augmenting excitatory sensory input and attenuating inhibitory prefrontal input to the amygdala (Rosenkranz and Grace, 2002). Systemic and local applications into the amygdala of D1 agonist and antagonist are known to potentiate and decrease fear response in animals, respectively. Although some studies reported that applications of D2 agonist and antagonist induced similar effects, the results were less consistent compared with D1-mediated effects (for review, see Pezze and Feldon, 2004; de la Mora et al., 2009).

A human functional magnetic resonance imaging (fMRI) study reported that doparminergic drug therapy such as levodopa or DA agonists partially restored amygdala response due to emotional task in Parkinson's disease patients who showed no significant amygdala response during drug-off states (Tessitore et al., 2002). In addition, another fMRI study of healthy volunteers has demonstrated that amphetamine potentiated the response of the amygdala during an emotional task (Hariri et al., 2002). More recently, Kienast et al. (2008) reported that dopamine storage capacity in human amygdala, measured with 6-[^{18}F]fluoro-L-DOPA positron emission tomography (PET), was positively correlated with functional magnetic resonance imaging (fMRI) signal changes in amygdala. However, the contribution of DA D1 and D2 receptors to amygdala response induced by affective stimuli is unknown in human. To investigate the relation between amygdala reactivity and dopamine receptor subtype, we conducted a multimodal *in vivo* neuroimaging study in which DA D1 and D2 receptor bindings in the amygdala were measured with PET, and amygdala response by novel faces with either neutral or fearful expression was assessed with fMRI. Based on animal pharmacological studies, we hypothesized that D1, but not D2 receptors, would predict amygdala response.

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Materials and Methods

Subjects

Twenty-one male volunteers [mean age 23.1 ± (SD) 3.6 years] were studied. They did not meet the criteria for any psychiatric disorder based on unstructured psychiatric screening interviews. None of the controls were taking alcohol at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. All subjects were right-handed according to the Edinburgh Handedness Inventory. All subjects underwent MRI to rule out cerebral anatomic abnormalities. After complete explanation of the study,

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

fMRI procedure

Stimulus materials were taken from the Karolinska Directed Emotional Faces (KDEF) (Lundqvist et al., 1998). Thirty neutral and 30 fear faces were used, with half of them being male faces. The pictures were projected via a computer and a telephoto lens onto a screen mounted on a head-coil. The experimental design consisted of 5 blocks for each of the 2 conditions (neutral, fear) interleaved with 21 s rest periods. The order of presentation for the 2 conditions (neutral and fear) was randomized. During the baseline condition, subjects viewed a crosshair pattern projected to the center of the screen. In each 21 s block, 6 different faces of the same emotional class were presented for 3.5 s each. During the scans, the subjects were instructed to judge the gender of each face using selection buttons.

fMRI scanning

The images were acquired with a 3.0 Tesla Excite system (General Electric). Functional images of 126 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to the blood oxygenation level-dependent (BOLD) contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; echo time, 50 ms; repetition time, 3500 ms; matrix, 64 × 64; field of view, 24 × 24 cm).

Analysis of fMRI data

Data analysis was performed with the statistical parametric mapping software package (SPM2) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (MathWorks). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans had a resolution of $2 \times 2 \times 2$ mm^3. Functional images were spatially smoothed with a three-dimensional isotropic Gaussian kernel (full-width at half-maximum of 8 mm). Low-frequency noise was removed by applying a high-pass filter (cutoff period = 128 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of t-statistic were calculated on a voxel-by-voxel basis.

We assessed the contrasts of fear and neutral minus baseline (F&N-B). A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. The contrast images were obtained from single-subject analysis and entered into the group analysis. A one-sample t test was applied to determine group response for each effect. Significant amygdala activations were identified if they reached the extent threshold of $p < 0.05$ corrected for multiple comparisons, with a height threshold of $p < 0.001$, uncorrected.

PET scanning

After the fMRI session, each participant underwent PET scanning. The interval between fMRI session and PET scan was 3–5 h. PET studies were performed on ECAT EXACT HR+ (CTI-Siemens). The system provides 63 planes and a 15.5 cm field of view. To minimize head movement, a head fixation device (Fixster) was used. A transmission scan for attenuation correction was performed using a germanium 68–gallium 68 source. Acquisitions were done in three-dimensional mode with the interplane septa retracted. For evaluation of D1 receptors, a bolus of 219.7 ± 6.9 MBq of [^{11}C]SCH23390 with specific radioactivities (95.7 ± 35.5 GBq/μmol) was injected intravenously from the antecubital vein with a 20 ml saline flush. For evaluation of extrastriatal DA D2 receptors, a bolus of 218.1 ± 14.7 MBq of [^{11}C]FLB457 with high specific radioactivities (221.6 ± 94.9 GBq/μmol) was injected in the same way. Dynamic scans were performed for 60 min for [^{11}C]SCH23390 and 90 min for [^{11}C]FLB457 immediately after the injection. All emission scans were reconstructed with a Hanning filter cutoff frequency of 0.4 (full-width at half-maximum, 7.5 mm). MRI was performed on Gyroscan NT (Philips Medical Systems) (1.5 T). T1-weighted images of the brain were obtained for all subjects. Scan parameters were 1-mm-thick, three-dimensional T1 images with a transverse plane (repetition time/echo time, 19/10 ms; flip angle, 30°; scan matrix, 256 × 256 pixels; field of view, 256 × 256 mm; and number of excitations, 1).

Quantification of DA D1 and D2 receptors

Quantitative analysis was performed using the three-parameter simplified reference tissue model (Lammertsma and Hume, 1996; Olsson et al., 1999). The cerebellum was used as a reference region because it has been shown to be almost devoid of DA D1 and D2 receptors (Farde et al., 1987; Olsson et al., 1999; Suhara et al., 1999). The model provides an estimation of the binding potential ($BP_{ND\ (nondisplaceable)}$) (Innis et al., 2007), which is defined by the following equation: $BP_{ND} = k_3/k_4 = f_2 B_{max}/\{K_d [1 + \Sigma_i F_i/K_{di}]\}$, where k_3 and k_4 describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, f_2 is the "free fraction" of nonspecifically bound radioligand in brain, B_{max} is the receptor density, K_d is the equilibrium dissociation constant for the radioligand, and F_i and K_{di} are the free concentration and dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996). Tissue concentrations of the radioactivities of [^{11}C]SCH23390 and [^{11}C]FLB457 were obtained from regions of interest (ROIs) defined on PET images of summated activity for 60 min and 90 min, respectively, with reference to the individual MRIs coregistered on summated PET images and the brain atlas. Given our hypothesis of amygdala activation during viewing novel neutral and fearful faces, ROIs were set on the bilateral amygdala. The method for defining the boundaries of the amygdala was adapted from previously described methods (Kates et al., 1997; Convit et al., 1999). In short, the amygdala ROIs consisted of three axial slices. The anterior and posterior boundaries were identified at the level of the optic chiasm and the temporal horn of the lateral ventricle, respectively. The superior and inferior-lateral boundaries were identified at the level of the mammalian body and the temporal lobe white matter and extension of the temporal horn, respectively. We also created parametric images of BP_{ND} using the basis function method (Gunn et al., 1997) to conduct voxelwise SPM analysis in addition to ROI analysis.

Statistical analysis

ROI correlation analysis. Estimates of percentage signal change of fear vs baseline condition were extracted from the amygdala for each participant using the MarsBaR toolbox (Brett et al., 2002). The bilateral amygdala ROIs were defined from the WFU-Pickatlas SPM tool (Maldjian et al., 2003) with the aal atlas (Tzourio-Mazoyer et al., 2002). Correlation between BP_{ND} of [^{11}C]SCH23390 and [^{11}C]FLB457 in the bilateral amygdala and bilateral amygdala fMRI signal change were calculated using SPSS.

Confirmatory SPM correlation analysis. Parametric images of BP_{ND} of [^{11}C]SCH23390 and [^{11}C]FLB457 were analyzed using SPM2. Exactly the same image preprocessings of normalization and smoothing that were used in fMRI data analysis were applied to parametric images of BP_{ND}. To conduct multimodality voxelwise correlation analysis between the BOLD signal and DA receptor binding, we used the biological parametric mapping toolbox for SPM (Casanova et al., 2007). Significant clusters were identified if they reached the extent threshold of $p < 0.05$ corrected for multiple comparisons, with a height threshold of $R > 0.6$ ($p < 0.003$ uncorrected).

Results

Since the face pictures consisted of Caucasian faces (racial outgroup), even novel neutral faces produced amygdala response in several participants (Hart et al., 2000; Schwartz et al., 2003), leading to a blunted contrast of fear minus neutral. Therefore, we combined neutral and fear conditions and used F&N-B contrast for analyses. Group analysis of F&N-B contrast revealed significant bilateral amygdala responses [right amygdala (26, 0, −26), $t = 4.43$, 93 voxels, left amygdala (−20, −2, −26), $Z = 4.96$, 101

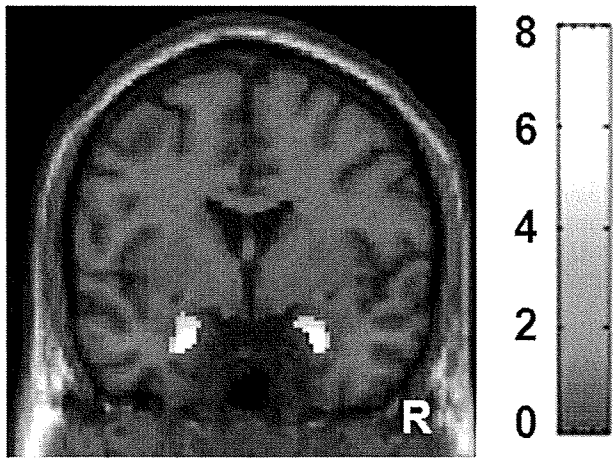

Figure 1. Images showing brain response induced by fear and neutral minus baseline condition. Bilateral amygdala responses are shown. The bar shows the range of the *t*-value. R indicates right.

voxels] (Fig. 1). The mean BP_{ND} of [^{11}C]SCH23390 in the right and left amygdala were 0.38 ± 0.08 and 0.39 ± 0.11, respectively. The mean BP_{ND} of [^{11}C]FLB457 in the right and left amygdala were 2.49 ± 0.50 and 2.50 ± 0.44, respectively.

Correlation analysis of biological parametric mapping revealed that the BP_{ND} value of [^{11}C]SCH23390 in the right amygdala was positively correlated with the BOLD signals in the right amygdala of F&N-B contrast [peak (28, 2, −28), 24 voxels] (Fig. 2A). ROIs analysis also revealed a similar significant correlation ($r = 0.59$, $p = 0.005$) in the right amygdala (Fig. 2B), but not in the left amygdala ($r = 0.18$, $p = 0.43$). According to biological parametric mapping analysis, the BP_{ND} value of [^{11}C]FLB457 in the amygdala was not correlated with BOLD signals in the amygdala of F&N-B contrast. ROIs analysis showed that right and left amygdala D2 binding was not correlated with the BOLD signals in the right ($r = 0.26$, $p = 0.27$) and left amygdala ($r = 0.28$, $p = 0.23$), respectively. Both biological parametric mapping analysis and ROIs analysis showed that D1 binding in the right and left amygdala was not correlated with D2 binding in the right ($r = 0.24$, $p = 0.30$) and left amygdala ($r = 0.16$, $p = 0.49$), respectively. We used anatomically defined ROIs of the amygdala rather than functional ROIs defined by fMRI in the ROI correlation analysis because it is difficult to place functionally defined ROIs on individual PET data. Anatomically defined ROIs of the amygdala were larger than functionally defined amygdala ROIs. This fact was advantageous in increasing the signal-to-noise ratio in the PET analysis, but led to blunted BOLD signal changes in the amygdala. However, BOLD signal changes derived from both ROI methods were highly correlated with each other. For example, very high correlation ($r = 0.80$, $p < 0.001$) was observed in the right amygdala. Thus, regardless of ROI definition method, we obtained similar results from ROI correlation analyses between BOLD signal changes and DA receptor binding in the amygdala.

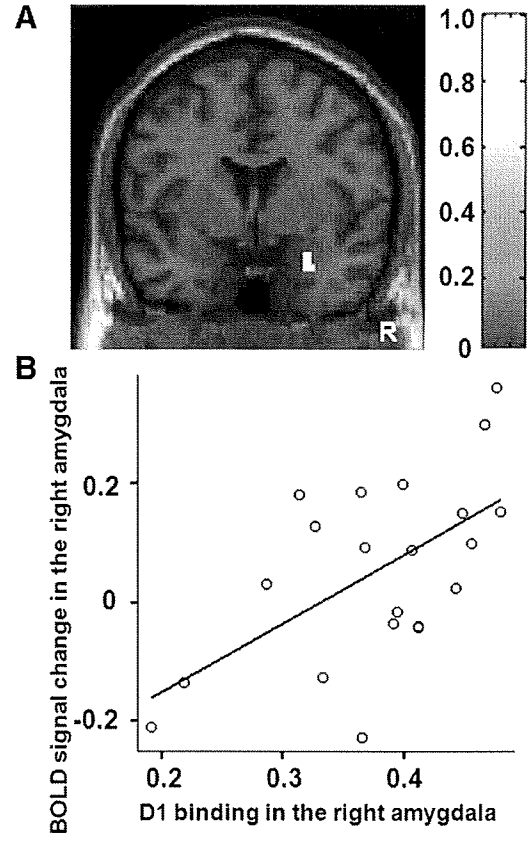

Figure 2. *A*, SPM correlation analysis revealed significant positive linear correlations between D1 binding in the right amygdala and right amygdala signal change. The bar shows the range of the correlation coefficient. *B*, ROI correlation analysis also revealed similar correlations. R indicates right.

Discussion

Using a multimodality *in vivo* neuroimaging approach, we first directly compared amygdala DA D1 and D2 receptor bindings, indices of receptor availability, with amygdala response evoked by novel or fearful stimuli in human. We found that DA D1 receptors, but not D2 receptors, predicted amygdala response induced by novel facial stimuli with either neutral or fearful expression. Our findings broaden our knowledge about dopaminergic transmission in amygdala response beyond the recent study (Kienast et al., 2008) that elucidated the relation between presynaptic dopamine synthesis and amygdala reactivity.

Human neuroimaging studies reported that DA potentiated amygdala response evoked by affective stimuli (Hariri et al., 2002; Tessitore et al., 2002). In rat studies, Rosenkranz and Grace (2002) demonstrated that DA enhances the response of the amygdala by augmenting excitatory sensory input via DA D2 receptor stimulation and attenuating inhibitory prefrontal input to the amygdala through DA D1 receptor stimulation. More recently, it was demonstrated that both D1 and D2 receptor stimulations directly enhanced the excitability of amygdala projection neurons via postsynaptic mechanism (Rosenkranz and Grace, 2002; Kröner et al., 2005; Yamamoto et al., 2007). Amygdala projection neurons are under inhibitory control by GABAergic interneurons (Royer et al., 1999). Both projection neurons and interneurons in the amygdala express DA D1 and D2 receptors (Rosenkranz and Grace, 1999). It has been shown that DA and D1 receptor stimulation augments interneuron excitability and increases the frequency of IPSC in amygdala projection neurons (Kröner et al., 2005). This is a counterintuitive result, considering the fact that DA disinhibits amygdala response *in vivo*. However, Marowsky et al. (2005) found that a subpopulation of amygdala interneurons (paracapsular intercalated cells), located between the major input and output stations of amygdala, is suppressed by DA through D1 receptor stimulation. DA D2 receptors also play a role in disinhibiting amygdala response by decreasing inhibi-

tion onto projection neurons and increasing inhibition onto interneurons (Bissière et al., 2003).

Although detailed examination of subnuclei of the amygdala is difficult in this imaging method, the dorsal portion of the amygdala roughly corresponds to the central nuclei of amygdala (CeA) and the ventral portion of the amygdala corresponds to the basolateral nuclei of amygdala (BLA) and intercalated cell masses (ICM) (Whalen et al., 2009). The amygdala clusters identified both in fMRI task effect analysis and in correlation analysis between D1 binding and amygdala reactivity were located in the ventral portion of the amygdala. Thus, our findings seem to mainly reflect BLA and ICM properties. It is worth mentioning that the highest density of D1 receptors within the amygdala was found in the ICM, followed by BLA, and the expression of D1 receptors is low in CeA (de la Mora et al., 2009; Muly et al., 2009). In contrast, D2 receptors are mainly distributed in CeA (de la Mora et al., 2009). Both D1 and D2 receptors are expressed both postsynaptically in dendrites and presynaptically in axon terminals (Pinto and Sesack, 2008; Muller et al., 2009; Muly et al., 2009), but D1 receptors in BLA are mainly expressed in the dendrites, indicating that DA directly modulates the excitability of BLA projection neurons and interneurons. At the same time, DA also acts on presynaptic D1 receptors to increase the probability of neurotransmitter release from glutamatergic terminals (Muly et al., 2009). Thus, the net DA effect on D1 receptors in the amygdala is a complex mixture of post- and presynaptic actions at several sites.

Although both DA D1 and D2 receptors contribute to potentiating amygdala response via various mechanisms as described above, our finding suggested that DA D1 receptors play a major role in the overall potentiation of amygdala response. At a behavioral level, previous animal studies repeatedly reported that D1 agonist and antagonist applications into the amygdala potentiated and decreased fear response, respectively. However, the effects of D2 agonist/antagonist on fear response have not been well established (Pezze and Feldon, 2004; de la Mora et al., 2009). Thus, the current finding could be regarded as being consistent with previous behavioral pharmacological studies. The combination of PET molecular imaging and fMRI seems to represent a powerful approach for understanding molecular functions in system neuroscience. However, this study has several limitations. First, current PET techniques for human do not have enough spatial resolution to distinguish subnuclei of the amygdala. Although analysis of parametric images of BP_{ND} has become well established (Gunn et al., 1997) and is used in many [^{11}C]SCH23390 and [^{11}C]FLB457 studies (Cervenka et al., 2006; Takahashi et al., 2008; Karlsson et al., 2009; McNab et al., 2009), a very small region or a single voxel is susceptible to partial volume effect. Thus, it is recommended that parametric image analysis should be used in combination with ROI analysis. At the same time, current results merit further investigation with a higher resolution PET scanner. Second, PET imaging cannot tell us the exact location of DA receptors expressed in projection neurons and interneurons. Future animal studies or *in vitro* studies would complement our findings to determine which D1 receptor-mediated mechanism is most responsible for the overall amygdala response. Third, differences in DA receptor occupancies by endogenous DA might affect BP, leading to different excitabilities of neurons. It is known that BP of [11C]SCH23390 is not sensitive to competitive endogenous dopamine even if massive dopamine is released by amphetamine (Abi-Dargham et al., 1999; Chou et al., 1999). However, it is possible that differences in receptor affinity might contribute to differences in DA receptor occupancies, although Farde et al. (1995) reported that variability in D2 receptor affinity is smaller than that in D2 receptor density. Finally, gender and race effects might also be possible. Any generalization should be approached with caution. Notwithstanding these limitations, we expect our finding to contribute to a broadening of the knowledge of the molecular mechanism of functional abnormalities of the amygdala implicated in neuropsychiatric disorders such as schizophrenia (Takahashi et al., 2004), depression (Drevets, 2000) and Parkinson's disease (Tessitore et al., 2002).

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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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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