The networks for the patients and controls were compared using the stacked model approach under the null hypothesis that a single estimate for each path coefficient is adequate for both groups, where instead of estimating a model for each group separately, the models are combined in a single program run (McIntosh and Gonzalez-Lima, 1994; Arbuckle and Wothke, 1995). The process involves statistically comparing functional models using the chi-square goodness-of-fit index of model fit, whereby path coefficients are constrained to be equal between conditions (null model) with those in which the coefficients are allowed to differ (alternative model). The comparison of models is made by subtracting the chi-square value for the alternative model from the chi-square value for the null model. If the alternative model, in which the coefficients were allowed to differ between groups, had a significantly lower chi-square value, then the coefficients that were allowed to vary between conditions were statistically different (McIntosh and Gonzalez-Lima, 1994). A P value of 0.05 (two-tailed) was chosen as the significant threshold.

3. Results

The t-test revealed that the BP value in the anterior cingulate was significantly different in patients with schizophrenia compared with normal controls (mean $\pm$ SD: controls, 1.17 ± 0.12, patients, 0.97 ± 0.17, $t_{27}=3.77$, $P=0.001$). There were no significant group differences in any other regions ($P>0.05$). In the analysis of structural equation modeling, our hypothesized model was valid and fit the data well under the null hypothesis that the model fit the data [$\chi^2(10)=16.4$, $P>0.09$, Akaike Information Criteria (AIC)=136.4]. The influence of

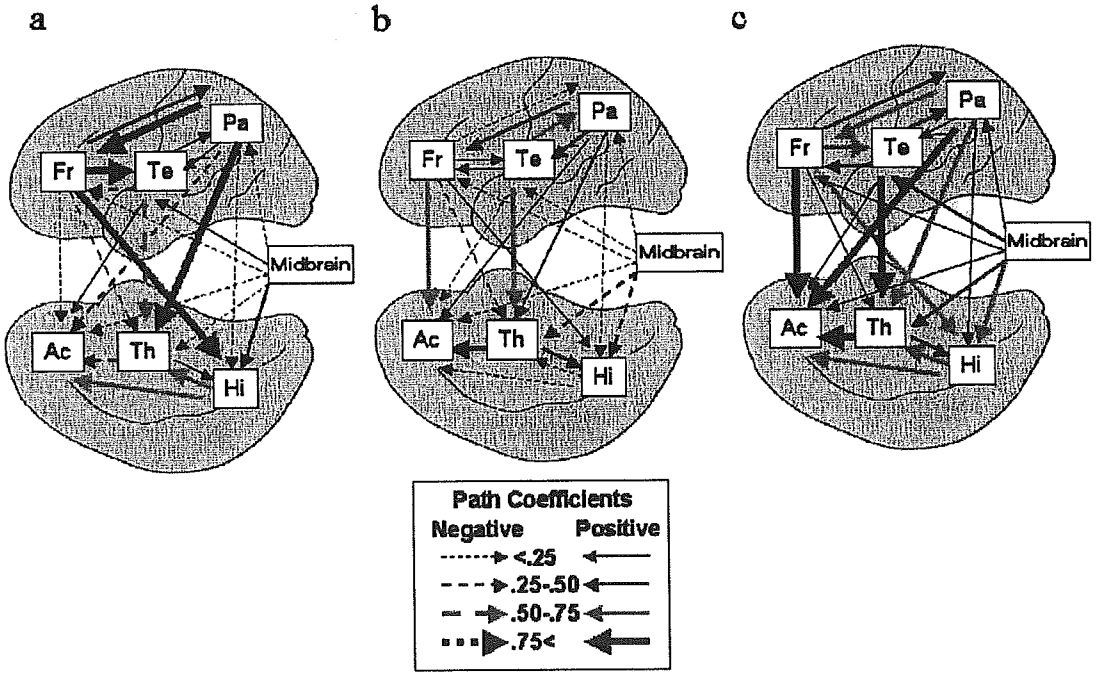

Fig. 4. Lateral and medial views of the human brains showing the functional networks reflecting on dopamine D2 receptor binding for each group, and the differences between groups. Arrows represent path coefficients. The arrow width for each path indicates the strength of each connection. Values for the width gradient are given in the box at the bottom. Positive path coefficients are shown as solid arrows, and negative path coefficients as dashed arrows. Differences are represented as the absolute values calculated by subtracting the coefficients for controls from those of patients. The width of the arrow indicates the magnitude of the difference. The color red indicates relatively large coefficients or differences (>0.75), and moderate coefficients or differences are indicated by the color orange (0.50–0.75). Path coefficients and their differences between groups are also shown in Table 3. Fr: Prefrontal cortex, Te: Temporal cortex, Pa: Parietal cortex, Hi: Hippocampus, Th: Thalamus, Ac: Anterior cingulate, Midbrain: Midbrain/Ventral tegmental area.

Table 2
Correlation matrices of regional BP in healthy control subjects and schizophrenic patients

	Fro	Tem	Par	Hip	Thal	Midbrain	Acing
Controls							
Fro	1.00						
Tem	0.87	1.00					
Par	0.84	0.83	1.00				
Hip	0.55	0.47	0.45	1.00			
Thal	0.15	0.07	0.29	0.46	1.00		
Midbrain	−0.26	−0.05	−0.17	0.25	0.10	1.00	
Acing	−0.37	−0.35	−0.55	−0.02	−0.37	0.11	1.00
Schizophrenics							
Fro	1.00						
Tem	0.52	1.00					
Par	0.53	0.73	1.00				
Hip	0.28	0.45	0.28	1.00			
Thal	0.06	0.53	0.45	0.33	1.00		
Midbrain	−0.18	0.61	−0.16	−0.47	−0.40	1.00	
Acing	0.71	0.64	0.71	0.17	0.57	−0.33	1.00

These values were the input for the path analysis, the results of which are shown in Table 3 and Fig. 4[a].

[a] Fro: Prefrontal cortex, Tem: Temporal cortex, Par: Parietal cortex, Hip: Hippocampus, Thal: Thalamus, Midbrain: Midbrain/Ventral tegmental area, Acing: Anterior cingulate.

alternative path connections did not improve the fit of the model.

Table 3 and Fig. 4 show the connectivity of the regional D2 receptor binding for each group (the correlations used are given in Table 2). The network model of the patients and normal subjects proved to be significantly different between the groups [$\chi^2_{diff}(23)=47.6$, $P<0.005$].

Normal subjects showed relatively large positive path coefficients (>0.75) from parietal cortex to frontal cortex and frontal cortex to temporal cortex among cortical regions, and frontal cortex to hippocampus and hippocampus to anterior cingulate. There were moderate positive coefficients (0.50–0.75) from hippocampus to thalamus and anterior cingulate, and negative coefficients from temporal cortex to thalamus (Table 3, Fig. 4, controls).

On the other hand, patients with schizophrenia showed different path coefficients from controls among regions. There were moderate positive path coefficients from temporal to parietal cortex, temporal

Table 3
Effects decomposition of inter-regional connections in the structural equation model of normal controls and patients[a]

Regions	Prefrontal cortex	Temporal cortex	Parietal cortex	Hippocampus	Thalamus	Anterior cingulate
Prefrontal cortex	–	0.82	0.26	0.75	−0.35	−0.24
	–	0.11	−0.02	0.24	−0.35	0.53
	–	0.71	0.28	0.51	0	0.77
Temporal cortex	−0.28	–	0.11	–	−0.60	0.11
	0.18	–	0.53	–	0.58	−0.07
	0.46	–	0.42	–	1.18	0.18
Parietal cortex	0.91	0.09	–	−0.14	0.80	−0.49
	0.41	0.29	–	−0.04	0.25	0.26
	0.50	0.20	–	0.10	0.55	0.75
Hippocampus	–	–	–	–	0.58	0.50
	–	–	–	–	−0.13	−0.12
	–	–	–	–	0.71	0.62
Thalamus	–	–	–	0.02	–	−0.35
	–	–	–	0.34	–	0.42
	–	–	–	0.32	–	0.77
Midbrain	−0.09	0.14	−0.07	0.31	−0.02	−0.10
	−0.07	−0.12	−0.03	−0.27	−0.35	−0.03
	0.02	0.26	0.04	0.58	0.33	0.07

Horizontal rows list structures being affected, and vertical columns list the origin of the effect. The effects not estimated are indicated by a dash (–). Bold characters represent moderate to large differences of coefficients (>0.50) between normal controls and patients with schizophrenia. Graphic representation of the network structure is shown in Fig. 4.

[a] Within each horizontal row, the upper value is the coefficient of normal controls, the middle value is that of patients, and the lower value is the absolute value calculated by the subtraction of the coefficients of controls from those of patients.

cortex to thalamus, and frontal cortex to anterior cingulate (Table 3, Fig. 4, patients).

The difference of path coefficients was presented as the absolute value calculated by subtraction of the coefficients for controls from those of patients (Table 3). Fig. 4 shows that there was a relatively large difference of path coefficients (>0.75) from frontal cortex, parietal cortex and thalamus to anterior cingulate, and from temporal cortex to thalamus. In addition, there were moderate differences of path coefficients (0.50–0.75) from prefrontal cortex and midbrain to hippocampus, hippocampus to thalamus and anterior cingulate, frontal cortex to temporal cortex, and parietal cortex to frontal cortex and thalamus (Table 3, Fig. 4, differences).

4. Discussion

This is the first study to apply structural equation modeling to data on regional receptor binding, which could be assumed to influence each other and change over the long duration of the disease via the structural network. The results indicated that the network model of the patients and normal subjects differed significantly between the groups.

As to the individual path coefficients, (a) effective connectivity between cortical regions was different between controls and patients; (b) connectivity from prefrontal cortex, parietal cortex, and thalamus to anterior cingulate in patients differed from that in controls; (c) there was no effective connectivity from prefrontal cortex to anterior cingulate and thalamus via the hippocampus in patients as observed in normal subjects; (d) a difference was also observed in the connectivity the temporal cortex and parietal cortex to thalamus, and from the midbrain/tegmental area to hippocampus. These results showed that patients exhibited an abnormality that was not evident in regional receptor binding but was evident through inter-regional connectivity of receptor systems.

This difference is not likely to be due to an effect of blood flow, since BP values from the reference tissue model are minimally dependent on tracer delivery (Lammertsma and Hume, 1996). We think that the scan represents not phasic but tonic dopamine and that there was almost no effect of stressors or internal/external stimuli during the PET scan, since our previous study revealed that extrastriatal [^{11}C]FLB457 was not sensitive to endogenous dopamine (Okauchi et al., 2001). In the previous study, we also found very good test–retest reproducibility for [^{11}C]FLB457 binding in repeated measurements under the same conditions as in this study (Sudo et al., 2001).

Although connecting tracts, including cortico–cortical and thalamo–cortical association fibers, utilize glutamate as a transmitter (Huntley et al., 1994), the dopaminergic and glutamatergic systems are closely integrated, as each modulates the activity levels of the other (Biggs and Starr, 1997). Dopaminergic neurons have input to inhibitory GABAergic neurons of the cortex, and "mis-wiring" of this input was indicated in patients with schizophrenia (Benes, 1997). Taking these findings into consideration, the connections between regional D2 receptor systems might reflect connections between dopamine and several other neurotransmitter systems and affect the dopaminergic tone among several brain regions. Their anomalies may reflect aberrant changes in the structural neuronal network regulating neurotransmitter systems and affect the connectivity of regional D2 receptor systems in patients with schizophrenia.

The absolute values of the path coefficients may indicate the strength of the influence between regions. As to the positive and negative signs of path coefficients, they showed the opposite influence of dopamine neurons from one region to another through the synaptic connections between dopamine and glutamatergic/GABAergic systems. This was supported by the suggestion that dopamine neurons were affected by glutamatergic neurons either directly or via GABAergic interneurons, acting as accelerators and brakes, respectively (Carlsson et al., 2000). However, an increase of post synaptic BP can result from an up-regulation to the decrease in the amount of dopamine or an adaptation to the increase in the amount of dopamine in the synaptic cleft. This does not allow a direct translation of path coefficients based on BP data as indices of excitation or inhibition of the dopaminergic systems. Path coefficients can indicate whether there are group-related differences in functional influences within the same anatomical pathways, but we must evaluate their neurophysiological meaning cautiously under the consideration of interpretative difficulties.

In schizophrenia, aberrant functional integration may appear through the systems-level neuronal changes reflected in the connectivity of regional D2 receptor binding. Aberrant connectivity from the prefrontal cortex, parietal cortex, and thalamus to the anterior cingulate was observed in schizophrenia patients. We considered that the regions without evident change in D2 receptors were also related to the pathophysiology of schizophrenia through aberrant neuronal connections by their effect on dopaminergic regulation in the anterior cingulate, where the change in dopamine D2 receptor binding was shown to be related to the positive symptoms of schizophrenia (Suhara et al., 2002).

Further, it was suggested that defective interactions of the cortico–cortical and cortico–thalamic network might underlie certain dysfunctions of conscious integration such as those seen in schizophrenia (Tononi and Edelman, 2000). The effective connectivity from the prefrontal cortex to limbic regions via the hippocampus observed in normal subjects may relate to normal information processing and cognitive memory function, and aberrant circuitry via the hippocampus may induce deficits in them (Benes, 2000; Fletcher, 1998).

The results suggest that a systems-level change reflected in the connectivity of regional D2 receptor binding was observed in patients with schizophrenia. This change may reflect imbalance and abnormal synaptic connections. However, a few confounding factors need to be considered when interpreting our results. Since the method is a modeling technique, it requires simplifying assumptions about the direction of influences and anatomy. Thus our results were affected by these constraints placed upon our assumptions, although the model fit the data well and the influence of alternative path connections did not improve the fit of the model.

The mean voxel values of the right and left VOIs were used to increase the signal-to-noise ratio for the calculations and to simplify the assumptions and the model regarding the direction of influences and anatomy. As shown in Table 1, the standard deviation in the thalamus and hippocampus was smaller when the values of right and left VOIs were averaged. In all regions, we found a relatively high correlation of the BP values of the right and left VOIs in each group ($r>0.90$), and there may be no serious problem concerning the averaging of the right and left VOIs in these regions. However, we found a trend of asymmetry of the BP values in the temporal regions of the patient group (paired t-test, $t=3.67$, $P<0.01$), and there was the possibility that averaging the right and left VOIs masked asymmetries in the patient group, limiting the conclusions drawn from the model.

Because of the limited number of patients and the moderate level of severity, it cannot be ruled out that, with a larger patient population, other connectivities might also show differences. Although FLB 457 has affinity for both dopamine D2 and D3 receptors, the anatomical distribution of D3 receptors supports the view that the [^{11}C]FLB 457 binding in our measured regions mainly represents binding to D2 receptors (Landwehrmeyer et al., 1993; Murray et al., 1994). Still, there is the possibility that our findings could be partly explained by a change in dopamine D3 receptors.

Although the striatum was regarded as important for the dopaminergic network, we could not evaluate it because of methodological problems. Although [^{11}C]FLB 457 accumulated to a high degree in the striatum, high-affinity ligands show very slow clearance from the high density receptor region where radioligand delivery can be rate-limiting (Farde et al., 1997; Suhara et al., 1999). The connectivity shown in this study may include the effect of unexamined critical regions behind our network model, and we think that our data are currently limited for drawing general conclusions, and future work with ligands better suited for the measurement of extensive brain regions is necessary to solve this problem.

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Effects of dopaminergic and serotonergic manipulation on emotional processing: A pharmacological fMRI study

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Recent neuroimaging studies have demonstrated abnormal central emotional processing in psychiatric disorders. The dopamine (DA) systems and serotonin (5-HT) systems are the main target of psychopharmacotherapy. DA D_2 receptor antagonists and selective serotonin reuptake inhibitors (SSRIs) are widely used in psychiatric practice. Investigating the effects of these drugs on emotional processing should lead to a better understanding of the pathophysiology and pharmacotherapy of neuropsychiatric disorders. We aimed to examine effects of dopaminergic and serotonergic manipulation on neural responses to unpleasant pictures in healthy volunteers using pharmacological fMRI.

Thirteen healthy male subjects participated in a single-blind, randomized, placebo-controlled design study. Each subject participated in three fMRI sessions. In each session, participants were orally administered either 25 mg of sultopride or 50 mg of fluvoxamine or placebo prior to scanning, and neural responses to unpleasant and neutral pictures were recorded.

Despite no significant differences being found in the subjective ratings of affective pictures across three sessions, compared to placebo, acute treatments of DA D_2 receptor antagonists and SSRIs commonly attenuated the amygdala activity, although both treatments had slightly different modulatory effects on other components of the neural circuit of emotional processing. This study has shown that even acute treatment of drugs that manipulate neurotransmitter systems could affect brain activation associated with emotional processing in human brain. At the same time, our findings suggest that pharmacological fMRI could be a powerful tool for investigating the neurophysiological properties of drugs targeting neuropsychiatric disorders.

Keywords: Pharmacological fMRI; Dopamine D_2 receptor antagonists; SSRIs; Emotion

Introduction

Recent neuroimaging studies have revealed abnormal central emotional processing in patients with psychiatric disorders such as mood disorders (Drevets, 2000), schizophrenia (Paradiso et al., 2003; Takahashi et al., 2004), and anxiety disorders (Kent and Rauch, 2003). However, the majority of patients examined in neuroimaging studies, especially those with schizophrenia, were taking drugs, and their possible effects on neural responses have not been clarified.

The dopamine (DA) systems and serotonin (5-HT) systems are the main target of pharmacological treatment of these psychiatric disorders. DA D_2 receptor antagonists and selective serotonin reuptake inhibitors (SSRIs) are widely used and tolerated in clinical practice as antipsychotics and antidepressants/anxiolytics, respectively. To investigate the effects of these drugs on emotional processing will give a better understanding of the pathophysiology of psychiatric disorders and the neurophysiological properties of drugs targeting neuropsychiatric disorders.

DA systems arise from two primary midbrain areas. The mesostriatal system originates from the substantia nigra pars compacta (A9) and innervates the striatum, whereas the mesocorticolimbic system originates mainly from the ventral tegmental area (A10) and innervates the amygdala, hippocampus, and frontal cortical areas (Pralong et al., 2002). The DA systems are extensively distributed throughout the network of the limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuit implicated in emotional processing (Drevets, 2000; Pralong et al., 2002). The components of the DA systems and LCSPT circuit overlap (Cardinal et al., 2002; Groenewegen and Uylings, 2000). Our PET study demonstrated that mesocorticolimbic regions (amygdala, hippocampus, thalamus, and anterior cingulate) are relatively rich in DA D_2 receptors, besides striatal regions (Okubo et al., 1999). Thus, DA D_2 receptor antagonists could be considered to

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substantially modulate emotional processing, particularly in the mesocorticolimbic systems. A recent study reported that acute administration of the DA D_2 receptor antagonist sulpiride impaired emotional memory, and the need for sensitive tests to study dopaminergic modulation of emotional processing was highlighted (Mehta et al., 2005).

Pharmacological fMRI is a non-invasive in vivo method that has the potential to investigate the effects of pharmacological manipulation on cognitive and emotional processing in the human brain, and this tool is expected to have a major impact on clinical practice and drug discovery (Honey and Bullmore, 2004). Among major neurotransmitter systems, DA systems have been widely investigated by the use of pharmacological fMRI. However, most pharmacological fMRI studies of DA systems have focused on cognitive or motor function, and pharmacological fMRI studies using emotional tasks are limited (Honey and Bullmore, 2004). An fMRI study has reported that dopaminergic drug therapy such as levodopa or DA agonists partially restored amygdala activation due to emotional task in Parkinson's disease (PD) patients who showed no significant amygdala activation during drug-off states (Tessitore et al., 2002). In addition, another fMRI study has demonstrated that amphetamine potentiated the response of the amygdala during an emotional task (Hariri et al., 2002a). Hence, using pharmacological fMRI, we aimed to investigate the effects of DA D_2 blockade on neural activity in the response to unpleasant pictures in healthy volunteers, hypothesizing that blockade of DA D_2 receptors would suppress the amygdala activity in response to emotional stimuli.

Another major neurotransmitter system, 5-HT systems, originates from 5-HT neurons in the raphe nuclei, and 5-HT fibers project to the amygdala, hippocampus, and frontal cortical area that are the key nodes of emotional processing (Buhot, 1997; Pineyro and Blier, 1999). Abnormally elevated amygdala activities in depressive patients have consistently been reported, and treatments by antidepressants such as SSRIs were reported to normalize the elevated amygdala activity (Drevets, 2000). Exaggerated amygdala responses were also reported in anxiety disorders (Rauch et al., 2003), and SSRIs are coming into use in the treatment of anxiety disorders (Kent et al., 1998).

Although it has long been thought that there is a delay of several weeks before a true antidepressant effect occurs, recent studies have led to the notion that antidepressants work within the first week (Posternak and Zimmerman, 2005), and several studies reported that even acute antidepressant treatment could facilitate positive emotional processing and work to redress negative biases in emotional processing (Harmer et al., 2003a,b). These results suggest that a single dose of an antidepressant can facilitate positive emotional processing and inhibit negative emotional processing. In fact, a recent evoked potential study has investigated the effects of acute treatment of SSRIs on emotional processing. In that study, acute administration of SSRIs attenuated cortical responses to unpleasant pictures and enhanced cortical responses to pleasant pictures (Kemp et al., 2004). However, evoked potential studies have a major limitation in that they cannot detect activity of subcortical structures. Since the amygdala receives dense serotonergic input from the raphe nuclei and has a high density of 5-HT transporters, it is considered to be a prime site for the anxiolytic action of SSRIs (Kent et al., 1998). Therefore, the need to investigate the effects of the acute administration of SSRIs on the amygdala is emphasized. We hypothesized that the acute administration of SSRIs, as well as DA D_2 antagonists, would suppress the response of the amygdala, a key node of negative emotional processing, and would modulate the response in the related brain area involved in negative emotional processing in healthy volunteers.

Methods

Participants

Thirteen healthy right-handed Japanese male subjects (mean age 29.2 ± 5.1 years, mean height 170.0 ± 4.1 cm, mean weight 65.5 ± 9.0 kg) were recruited from the surrounding community. They did not meet the criteria for any psychiatric disorder. 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 underwent an 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 Committee.

Materials

Stimulus materials were taken from the International Affective Picture System (IAPS) (Lang et al., 1997). Neutral and unpleasant pictures were selected according to the subjective ratings provided by IAPS. We employed 48 pictures from each class. Slides of the two emotional classes were matched for content (faces, human figures, animals, objects, scenery). The pictures were projected via a computer, and a telephoto lens onto a screen mounted on a head-coil. The experimental design consisted of 6 blocks for each of the 2 conditions (neutral, unpleasant) interleaved with 24-s rest periods. The order of presentation for the 2 conditions was fixed in the neutral–unpleasant sequence.

During the rest condition, subjects viewed a crosshair pattern projected to the center of the screen. In each 24-s block, 8 different pictures of the same emotional class were presented for 3 s each. During the scans, the subjects were instructed to press a selection button with the right index finger, indicating how each picture made them feel using a 3-point analog scale (1 = neutral, 2 = slightly unpleasant, 3 = extremely unpleasant).

Physical data

Participants were checked for blood pressure (BP), heart rate (HR), and respiration rate (RR) before administrations of drugs and just before scanning.

Drug administration

We used sultopride (SUL), a substituted benzamide derivative, as a selective DA D_2 receptor antagonist. SUL has higher lipophilicity than other substituted benzamide derivatives such as amisulpride or sulpiride and penetrates the blood–brain barrier more easily (Kapur et al., 2002; Mizuchi et al., 1983; Moller, 2003). For this reason, we used SUL with the purpose of minimizing the effect of DA D_2 receptor antagonist on peripheral DA receptors in blood vessels or the pituitary, which are outside the blood–brain barrier. The dosage of SUL was determined by our recent positron emission tomography (PET) study, in which the ED_{50} (concentration required to induce 50% occupancy) value of

SUL was 8.7 mg for dose and 32 ng/ml for plasma concentration, and 25 mg of SUL resulted in sufficient plasma concentration to occupy approximately 60–70% of dopamine D_2 receptors (unpublished data). It has been shown that occupancy in the approximate range of 60–70% of central dopamine D_2 receptors is needed to produce an antipsychotic effect. Higher receptor occupancy (more than 80%) is associated with extrapyramidal effects (Farde et al., 1992; Kapur et al., 2000). Since DA D_2 receptor antagonists are mainly used with the purpose of obtaining antipsychotic effects, we aimed to elucidate the effects of occupancy of about 60–70% of central DA D_2 receptors in this study. We used 50 mg of fluvoxiamine (FLU) as SSRI. A previous study reported that minimally effective dosage was 50 mg/day (Walczak et al., 1996), and our previous data demonstrated that the ED_{50} value of FLU was 7.4 mg for dose and 4.2 ng/ml for plasma concentration and that 50 mg of FLU resulted in enough plasma concentration to occupy approximately 80% of 5-HT transporters (Suhara et al., 2003).

The study was a single-blind, randomized, placebo-controlled cross-over design. Each subject participated in three fMRI sessions separated by a minimum washout period of 14 days. Because it was reported that the elimination half-life of SUL in plasma was 3.6 h (Kobari et al., 1985) and that of FLU was 15 h in human (DeVane and Gill, 1997), it was considered that a 14-day washout period was sufficient and that the order of the drugs did not affect the plasma concentration of each drug. In each session, participants were given orally either 25 mg of SUL or 50 mg of FLU or placebo (PBO) (lactose) prior to scanning in a single-blind manner so that appropriate medical treatment could be administered in the event of adverse responses. The order of drug administration was counterbalanced across the subjects. The drug administration order consisted of 6 combinations (SUL–FLU–PBO, SUL–PBO–FLU, FLU–SUL–PBO, FLU–PBO–SUL, PBO–SUL–FLU, and PBO–FLU–SUL), and we randomly assigned each of the combinations to each subject. To ensure maximum and stable plasma concentrations of SUL and FLU, SUL and PBO were given 2 h before scanning, and FUL was given 5 h prior to scanning.

Images acquisition

The images were acquired with a 1.5 T Signa system (General Electric, Milwaukee, WI). Functional images of 264 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to the blood oxygenation level dependent (BOLD) contrast. Each volume consisted of 30 transaxial contiguous slices with a slice thickness of 4 mm to cover almost the whole brain (flip angle, 90°; TE, 50 ms; TR, 3 s; 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 (SPGR), 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 statistical parametric mapping software package (SPM02) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA). 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 × 2 × 2 mm^3. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (full width at half maximum of 8 mm). Low frequency noise was removed by applying a high-pass filter (cutoff period = 192 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 convoluted with a hemodynamic response function. Statistical parametric maps for each contrast of t statistic were calculated on a voxel-by-voxel basis. The t values were then transformed to unit normal distribution, resulting in Z scores.

To assess the specific condition effect, we used the contrasts by subtracting the BOLD signals in response to the neutral condition from those in response to the unpleasant condition (U–N contrast) in single-subject analysis. For each drug treatment condition, the U–N contrast images obtained from single-subject analysis were entered into group analysis. A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization for the population from which data are obtained. A one-sample t test was used to determine group activation for each drug. To compare the effect of drugs on the U–N contrast, we performed paired t tests (SUL vs. PBO, FLU vs. PBO, PBO vs. SUL, and PBO vs. FLU) to test relative differences in the pattern of neural activation by subtracting the unpleasant minus neutral U–N contrasts of PBO treatment from the U–N contrasts of drug (SUL/FLU) treatments and vice versa. Significant clusters of activation were determined using the conjoint expected probability distribution of the height and extent of Z scores with the height and extent threshold. Coordinates of activation were converted from MNI coordinates to the Talairach and Tournoux coordinates using the mni2tal algorithm (M. Brett, Cambridge, MA) (Talairach and Tournoux, 1988).

To examine individual differences in the effect of the two drugs on amygdala activation, we plotted the signal changes elicited by unpleasant condition compared to neutral condition in the amygdala. We used signal changes of the left amygdala (x, y, z = −14, −3, −22) and the right amygdala (x, y, z = 22, −3, −15), showing the largest signal reduction by SUL treatment as revealed by group analysis (paired t test). Similarly, we examined the signal changes of the left amygdala (x, y, z = −24, −12, −11) and the right amygdala (x, y, z = 26, 1, −22) for FUL treatment. We compared the mean signal changes in the left amygdala (x, y, z = −24, −12, −11) and the right amygdala (x, y, z = 26, 1, −22) elicited by unpleasant condition compared to neutral condition during PBO treatment and drug (SUL and FLU) treatments.

Results

Physical data

Two-way repeated-measures analysis of variance of BP (max), BP (min), HR, and RR showed no significant main effect of drug (P = 0.485, P = 0.744, P = 0.580, P = 0.556) nor a significant main effect of time (P = 0.514, P = 0.466, P = 0.248, P = 0.673) or

interaction ($P = 0.165$, $P = 0.123$, $P = 0.637$, $P = 0.683$), respectively.

Self-rating

Two-way repeated-measures analysis of variance of the ratings showed a significant main effect of condition ($P < 0.001$) but not a significant main effect of drug ($P = 0.66$) or interaction ($P = 0.59$). In other words, the mean ratings of unpleasant pictures were significantly greater than those of neutral pictures across the treatment group.

fMRI result

During PBO treatment, unpleasant condition relative to neutral U–N contrast revealed greater activations in the visual cortex, dorsal lateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), parietal cortex, insula, amygdala, thalamus, globus pallidus, and brainstem. During SUL treatment, U–N contrast revealed greater activations in the visual cortex, DLPFC, medial prefrontal cortex (MPFC), OFC, parietal cortex, hippocampus, thalamus, caudate body, and brainstem. During FUL treatment, U–N contrast revealed greater activations in the visual cortex,

Table 1
Brain activation in unpleasant condition relative to neutral condition during PBO, SUL, and FLU treatment

Brain region	Coordinates			BA	Z score	t value	Voxels
PBO							
R. visual cortex (LG, Cu, MOG, IOG, FG, MTG)	48	−66	−5	17, 18, 19, 37, 39	5.76	14	5404
L. visual cortex (LG, Cu, MOG, IOG, FG, MTG)	−44	−80	−3	17, 18, 19, 37, 39	5.29	11.02	
R. DLPFC (MFG, IFG)	46	15	32	9	4.53	7.65	331
L. DLPFC (IFG)	−51	7	33	9	3.82	5.5	53
R. OFC (IFG)	38	26	−18	47	3.49	4.73	59
R. OFC (IFG)	48	19	−8	47	3.27	4.27	27
L. OFC (IFG)	−36	17	−13	47	3.24	4.22	18
R. parietal cortex	30	−58	49	7	4.1	6.28	44
L. insula	−40	9	−6	13	3.36	4.47	31
R. amygdala	18	−3	−15		3.77	5.38	48
L. amygdala	−10	−1	−17		4.03	6.07	104
R. thalamus, GP	14	−2	7		3.71	5.24	66
L. thalamus, GP	−10	2	4		3.95	5.86	78
Brainstem	−4	−33	−2		4.78	8.61	356
SUL							
R. visual cortex (LG, Cu, MOG, IOG, FG)	26	−90	−4	17, 18, 19, 37	4.25	6.71	1109
L. visual cortex (LG, Cu, MOG, IOG, FG)	−28	−91	12	17, 18, 19, 37	4.97	9.45	1537
R. DLPFC (MFG, IFG)	50	26	15	8, 9, 46	4.17	6.47	673
L. DLPFC (IFG)	−48	17	23	9	4.04	6.1	377
MPFC (SFG, MFG, CG)	−2	31	41	8, 32	3.96	5.89	286
MPFC (SFG, MFG,)	−2	50	27	9	3.7	5.22	37
L. OFC (IFG)	−38	15	−11	47	3.48	4.7	45
R. OFC (MFG, IFG)	26	30	−18	11, 47	3.84	5.56	156
R. parietal cortex	32	−60	51	7	3.64	5.07	40
L. hippocampus, PHG	−28	−20	−7	27	4.28	6.82	94
R. thalamus	8	−19	8		4.26	6.76	732
L. thalamus, caudate body	−6	−17	6		4.16	6.44	
Brainstem	−2	−29	−5		4.15	6.42	
FLU							
R. visual cortex (LG, MOG, IOG, FG)	44	−71	−13	18, 19, 37	4.61	7.96	1623
L. visual cortex (LG, Cu, MOG, IOG, FG, ITG)	−38	−86	−4	17, 18, 19, 37	5.33	11.28	2154
R. DLPFC (MFG, IFG)	51	19	34	8, 9	4.44	7.34	323
R. DLPFC (IFG)	48	30	13	46	3.63	5.05	43
L. DLPFC (MFG, IFG)	−44	9	27	9, 46	4.05	6.12	273
R. parietal cortex	18	−73	48	7	3.95	5.84	43
R. parietal cortex	30	−56	49	7	3.86	5.62	123
L. parietal cortex	−30	−57	54	7	4.08	6.2	90
R. thalamus	10	−15	12		3.65	5.1	33
L. thalamus, caudate body	−10	−17	12		3.75	5.34	99
R. GP	14	2	4		3.58	4.93	48
Brainstem	−6	−28	−19		4.25	6.73	28

Significant differences were recognized at a height threshold ($P < 0.001$, uncorrected) and extent threshold (10 voxels). Coordinates and Z score refer to the peak of each brain region. BA = Brodmann area; L = left; R = right; LG = lingual gyrus; Cu = cuneus; MOG = middle occipital gyrus; IOG = inferior occipital gyrus; FG = fusiform gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; SFG = superior frontal gyrus; MFG = medial frontal gyrus; IFG = inferior frontal gyrus; CG = cingulate gyrus; AC = anterior cingulate; DLPFC = dorsal lateral prefrontal cortex; MPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; GP = globus pallidus.

DLPFC, parietal cortex, thalamus, caudate body, globus pallidus, and brainstem (Table 1 and Fig. 1). Compared to PBO, SUL treatment decreased responses of U–N contrast in the visual cortex, left temporal cortex, anterior cingulate, left amygdaloid–hippocampal region, cerebellum, and midbrain, whereas SUL treatment produced greater activation in the frontal cortex including DLPFC, MPFC, temporal cortex, parietal cortex, left insula, and left claustrum (Table 2 and Fig. 2). On the other hand, compared to PBO, FLU treatment decreased responses of U–N condition in the left OFC, right temporal cortex, right insula, right hippocampal region and left amygdaloid–hippocampal region, and right putamen, whereas FUL treatment produced greater activation in the temporal cortex and parietal cortex (Table 3 and Fig. 3).

During both SUL and FLU treatments, mean signal changes elicited by unpleasant condition compared to neutral condition were significantly less than those during PBO treatment ($t = 2.63$, $P = 0.02$ and $t = 2.93$, $P = 0.01$, respectively) in the left amygdala, but not the right amygdala ($t = 0.57$, $P = 0.57$ and $t = 1.93$, $P = 0.07$, respectively). The differences in mean signal changes between SUL and PBO were 0.36 (95% CI, 0.08–0.65) in the left amygdala and 0.07 (95% CI, −0.18–0.32) in the right amygdala. The differences in mean signal changes between FLU and PBO were 0.24 (95% CI, 0.07–0.41) in the left amygdala and 0.25 (95% CI, −0.17–0.52) in the right amygdala (Fig. 4).

Discussion

We found that acute administration of a therapeutic dose of DA D_2 antagonists and SSRIs had modulatory effects on emotional processing in the human brain, although the subjects recruited the entire neural network of the limbic–cortical–striatal–pallidal–thalamic circuit in response to unpleasant pictures while taking PBO. Our findings indicate that both acute SUL and FLU treatments manipulated the responses of the components of the circuit and commonly attenuated the activation of amygdala, a key node of the circuit.

DA D_2 receptor antagonist treatment decreased responses in the limbic areas (amygdala, hippocampus, anterior cingulate) along with the visual sensory cortex, cerebellum, and midbrain. Not

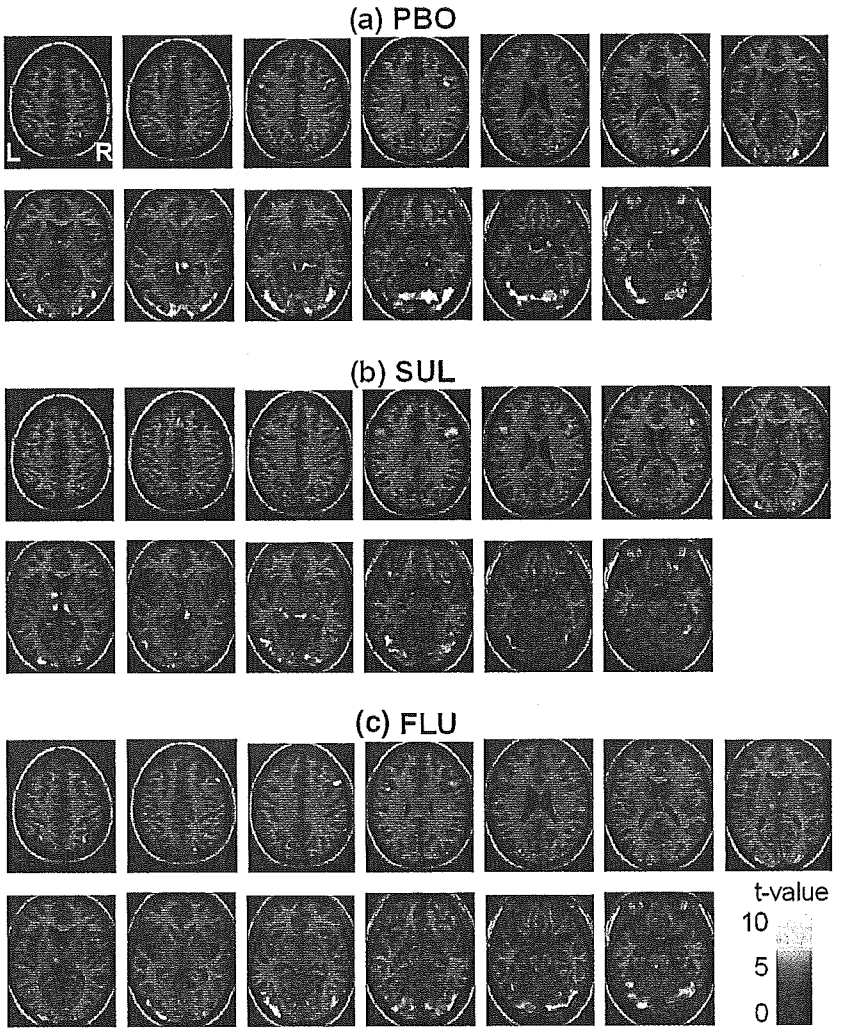

Fig. 1. Images showing dissociable brain activations in unpleasant condition relative to neutral condition during PBO treatment (a), SUL treatment (b), and FLU treatment (c). Significant differences were recognized at a height threshold ($t > 3.93$; $P < 0.001$, uncorrected) and extent threshold (10 voxels). The bar shows the range of the t value. Within the images, L indicates left and R indicates right.

Table 2
Brain regions showing significant effects of SUL treatment on neural activations in response to unpleasant condition relative to neutral condition

Brain region	Coordinates			BA	Z score	t value	Voxels
	x	y	z				
PBO vs. SUL							
L. occipital cortex (LG), cerebellum	−14	−72	−8	18	3.25	4.24	201
L. occipital cortex (Cu)	0	−62	5	30	3.43	4.6	33
L. occipital cortex (Cu)	−8	−78	33	19	3.34	4.42	13
L. occipital cortex (Cu)	−8	−70	16	31	2.96	3.69	12
L. occipital cortex (IOG)	−48	−78	−4	18	3.28	4.29	20
R. occipital cortex (Cu)	20	−92	30	19	2.96	3.7	10
L. temporal cortex (STG)	−34	16	−32	38	3.2	4.13	19
R. AC	2	34	22	32	3.18	4.1	11
L. PHG	−32	−30	−22	36	3.39	4.53	10
L. amygdala	−14	−2	−26		2.91	3.61	10
Midbrain	−10	−12	−15		3.38	4.5	19
SUL vs. PBO							
R. DLPFC (IFG)	55	30	8	46	3.19	4.12	24
L. DLPFC (MFG)	−53	17	25	9	2.88	3.55	14
L. DLPFC (IFG)	−50	5	27	9	3.01	3.77	22
MPFC (MFG)	8	29	45	8	3.17	4.08	29
R. frontal cortex	6	−32	55	4,5	2.96	3.69	46
R. frontal cortex (MFG)	26	−7	48	6	3.69	5.19	137
R. frontal cortex (MFG)	38	46	−6	10	3.17	4.08	35
R. frontal cortex (IFG)	46	22	15	45	3.79	5.44	50
L. frontal cortex (IFG)	−53	22	4	45	3.16	4.07	25
R. temporal cortex (MTG)	55	−49	−3	37	3.63	5.06	15
R. temporal cortex (MTG)	50	−33	0	21	3.16	4.06	53
L. temporal cortex (STG)	−51	−31	3	22	3.48	4.7	48
L. temporal cortex (MTG)	−55	−6	−13	21	3.25	4.24	21
R. parietal cortex	42	−47	41	40	3.62	5.03	88
R. parietal cortex	42	−30	55	40	3.15	4.04	23
R. parietal cortex	50	−13	47	3	3	3.76	19
L. parietal cortex	−38	−32	53	40	2.99	3.75	22
L. parietal cortex	−30	−42	48	40	2.97	3.71	10
L. insula	−48	−9	15	13	3.24	4.22	58
L. claustrum	−38	−25	0		3.27	4.28	93

To compare the effect of SUL on the U−N contrast, paired *t* tests (PBO vs. SUL and SUL vs. PBO) were conducted. Significant differences were recognized at a height threshold ($P < 0.005$, uncorrected) and extent threshold (10 voxels). See Table 1 legend.

surprisingly, attenuation of amygdala response by DA D_2 antagonists was in contrast to the previous pharmacological fMRI study where pharmacotherapy such as levodopa or DA agonists restored the amygdala activation in PD patients (Tessitore et al., 2002). However, the mechanisms underlying these results are not straightforward since DA could potentiate both the excitatory and inhibitory influences of afferent inputs on target neurons (Cohen et al., 2002).

Our PET study demonstrated that DA D_2 receptors are relatively dense in the mesocorticolimbic regions (amygdala, hippocampus, thalamus, and anterior cingulate), besides the striatal regions (Okubo et al., 1999). Considering the regional distributions of DA D_2 receptors, decreased activations in the amygdala, hippocampus, and anterior cingulate by DA D_2 receptor blockade indicate that the net effect of DA D_2 receptor activation is to enhance excitability of limbic regions in response to unpleasant stimuli, although we did not observe significant change of activation in the thalamus and striatal regions.

On the contrary, DA D_2 receptor blockade produced greater activations extensively in the cortical areas (frontal, temporal, and parietal). These enhanced activations in cortical areas are quite puzzling. A possible explanation is that SUL acute treatment might have increased dopaminergic transmission in the cortical area. DA D_2 antagonists are known to increase activity of A9 and A10 neurons through the feedback mechanism of presynaptic D_2-like autoreceptors (Westerink, 2002). Another substituted benzamide derivative, amisulpride, has been suggested to enhance cortical dopaminergic transmission through its preferential blockade of presynaptic D_2-like autoreceptors at optimal dose (Moller, 2003). We revealed that the registered clinical dose of SUL (300–600 mg, max 1800 mg) was about ten times higher than the estimated optimal dose by PET (unpublished data). Thus, if we used SUL at the optimal dose, it would act like amisulpride to enhance cortical dopaminergic transmission in the cortical regions.

Among the enhanced cortical areas, greater activations in the PFC are noteworthy since it is considered to be a main modulator in the neural circuit of emotional processing (Davidson et al., 2002; Drevets, 2000). There are direct and indirect connections between the amygdala and PFC (Groenewegen and Uylings, 2000; Price et al., 1996), and the PFC can attenuate amygdala activation via these connections (Hariri et al., 2000; Rosenkranz and Grace, 1999, 2001). Cognitive demands such as explicit and elaborate evaluation of stimuli that are mediated in the PFC are known to attenuate automatic amygdala activation (Hariri et al., 2000; Phan et al., 2002). In this sense, passive viewing is the ideal way to examine robust amygdala activation, but the behavioral data during the scans should be recorded. To reconcile this dilemma, we used the current paradigm, in which the participants roughly reported their subjective experience, aiming to ensure minimal cognitive demands. Since cognitive demands across the 3 sessions were identical in this design, we can rule out the effect of cognitive demands when interpreting the attenuated amygdala activation, but it remains possible that attenuated amygdala activity is partially attributable to secondary change to the principal drug effect on the PFC. However, since we observed the net effects of direct drug effect on the amygdala and possible secondary modulation by afferent input in the amygdala, we cannot differentiate between these possible mechanisms in this study.

SSRI treatment also decreased the activation in amygdaloid–hippocampal regions, as we predicted. However, unlike DA D_2 receptor antagonists, SSRI treatment reduced activation in different areas such as OFC, basal ganglia, and insula but not in the visual cortex. Moreover, SSRI treatment produced greater activation only in the temporal cortex and parietal cortex, not in the frontal cortex. Although both DA D_2 antagonist and SSRI treatment resulted in common inhibitory effects on activations of amygdaloid–hippocampal regions, the different patterns observed in other regions strongly point to different mechanisms underlying the common effects.

FLU was approved for the treatment of obsessive-compulsive disorder (OCD) but has not been officially approved for the treatment of depression in the United States. However, it is approved in many countries for the indication of depression (Hachisu and Ichimaru, 2000). It is probably no less effective than the other SSRIs in treating depression (Dalery and Honig, 2003) and no better than the other SSRIs at treating OCD (Mundo et al., 1997). FLU has greater selectivity for 5-HT vs. noradrenaline (NA) than fluoxetine and paroxetine and less selectivity than citolopram and sertraline (Wong and Bymaster, 2002). A microdialysis study

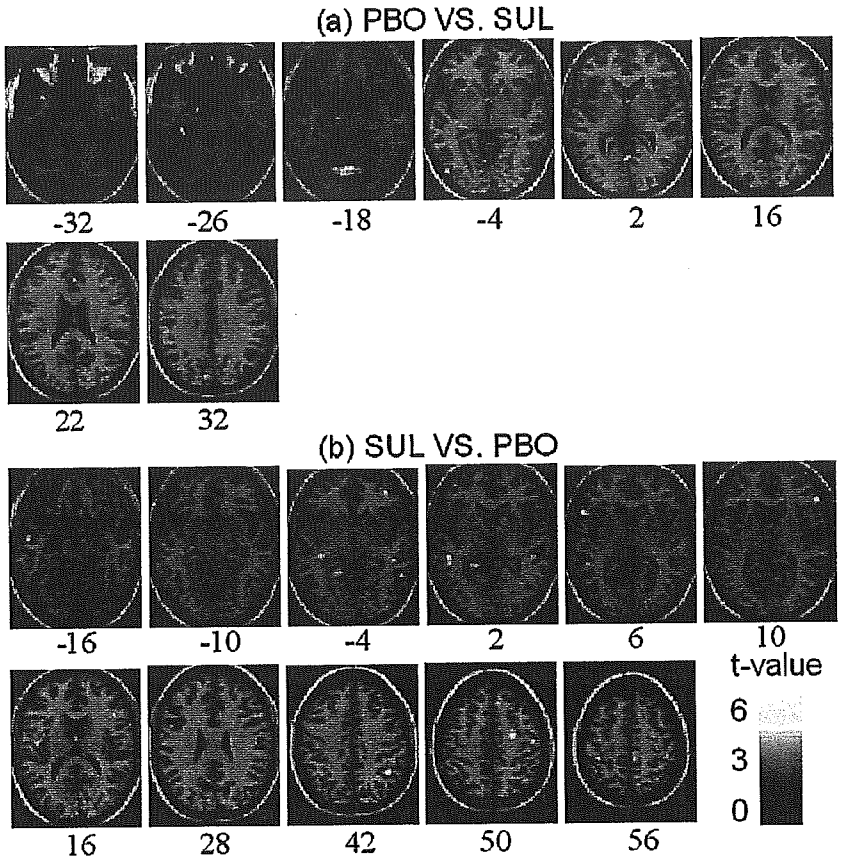

Fig. 2. Images showing manipulated brain activations in response to unpleasant condition relative to neutral condition under SUL treatment. Compared to PBO, attenuated activations were shown in the visual cortex, left temporal cortex, anterior cingulate, left amygdaloid–hippocampal region, cerebellum, and midbrain (a). Enhanced activations were found in the frontal cortex, temporal cortex, parietal cortex, left insula, and left claustrum (b). Significant differences were recognized at a height threshold ($t > 3.05$; $P < 0.005$, uncorrected) and extent threshold (10 voxels). The bar shows the range of the t value. Within the image, L indicates left and R indicates right. Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

demonstrated that SSRIs (FLU, citalopram, sertraline, and paroxetine) did not increase NA and DA extracellular levels in the PFC, and only acute administration of fluoxetine, which has modest selectivity for 5-HT vs. NA compared with other SSRIs, increased them (Bymaster et al., 2002). Therefore, when FLU was administered acutely, the potential effect on the NA or DA system might be negligible in this study.

We understand that the effects of acute SSRI treatment on 5-HT neurotransmission are complex due to the presence of autoreceptors on the presynaptic neuron. The distribution of 5-HT transporters closely matches the regional distribution of 5-HT nerve terminal and cell bodies. They are highly expressed in the amygdala, hippocampus, thalamus, striatum, and midbrain. Intermediate density is found in the cortex and cerebellum (Parsey et al., 2000). Blockade of 5-HT transporters by acute SSRI administration preferentially increases extracellular 5-HT in the raphe nuclei. An increase in somatodendric extracellular 5-HT activates 5-HT_{1A} autoreceptor feedback system to inhibit 5-HT release in terminal projection regions (Pineyro and Blier, 1999). However, preclinical microdialysis studies have consistently reported that acute systemic administration of SSRIs increased extracellular 5-HT concentrations in the raphe nuclei, frontal cortex, hippocampus, and amygdala (Bosker et al., 1995, 2001; Dawson and Nguyen, 1998; Hatanaka et al., 2000; Invernizzi et al., 1995; Malagie et al., 1995). In the present study, acute SSRI administration might have increased 5-HT neurotransmission at postsynaptic 5-HT receptors in the amygdaloid–hippocampal regions because postsynaptic 5-HT receptors are rich in the amygdala and hippocampus (Buhot, 1997; Pineyro and Blier, 1999) and an increase of 5-HT reduced reactivity of the amygdala to sensory inputs (Stutzmann et al., 1998). There are several 5-HT receptor subtypes expressed in the amygdala, and there are both inhibitory (e.g. 5-HT_{1A}) and excitatory (e.g. $5\text{-HT}_{2A}/5\text{-HT}_{2C}$) receptors (Stein et al., 2000). In addition, because excitatory and inhibitory neurons are tightly interconnected in the local circuits, it is unlikely that a large increase in inhibition can be observed without a concomitant increase in excitation. Therefore, we cannot differentiate specific 5-HT receptor subtype effects in this study and what we observed here was the net effect of 5-HT transmission change on the amygdala.

Although the putative anxiolytic and antidepressant effect of SSRIs is generally understood to be associated with a net increase in 5-HT neurotransmission, there are conflicting results on the function of 5-HT in anxiety. Several animal studies in the literature have demonstrated that high 5-HT was associated with anxiety, indicating a major role of 5-HT in the amygdala in the generation of anxiogenic behaviors (Chaouloff, 2000; Graeff et al., 1996). On the other hand, the fact that the success of the treatment with SSRIs and acute tryptophan depletion worsens depressive symptoms in depression suggests that an increase in 5-HT transmission may be

Table 3
Brain regions showing significant effects of FLU treatment on neural activations in response to unpleasant condition relative to neutral condition

Brain region	Coordinates			BA	Z score	t value	Voxels
	x	y	z				
PBO vs. FLU							
L. OFC (IFG)	−32	26	−15	47	3.05	3.85	16
R. temporal cortex (STG)	63	−34	11	22	3.8	5.47	52
R. insula	48	1	10	13	3.45	4.64	27
R. PHG	22	−17	−21	28	3.28	4.29	29
R. hippocampus	26	−11	−16		3.5	4.75	35
L. amygdala, hippocampus	−24	−12	−11		3.6	4.99	84
R. putamen	28	−2	−3		2.91	3.61	13
FLU vs. PBO							
R. temporal cortex (MTG)	59	−47	−8	37	3.49	4.74	49
R. temporal cortex (MTG)	55	−29	−5	21	3.08	3.92	46
R. temporal cortex (STG)	48	−18	−6	22	3.14	4.02	17
L. temporal cortex (STG, MTG)	−51	−39	6	22	3.2	4.14	31
L. parietal cortex	−24	−72	39	7	3.84	5.57	62
L. parietal cortex	−46	−32	51	40	3.32	4.38	44

To compare the effect of FLU on the U−N contrast, paired t tests (PBO vs. FLU and FUL vs. PBO) were conducted. Significant differences were recognized at a height threshold ($P < 0.005$, uncorrected) and extent threshold (10 voxels). See Table 1 legend.

anxiolytic in humans (Kent et al., 1998). Preclinical studies reported that emotional stress increases 5-HT concentration in the amygdala and prefrontal cortex (Amat et al., 2005; Kawahara et al., 1993), and an increase of 5-HT reduces reactivity of the amygdala to excitatory sensory inputs (Stutzmann et al., 1998). This has led to the suggestion that 5-HT may act as a constraint system to inhibit primitive and impulsive reaction by reducing responsiveness of lower brain centers to emotional stress (Kent et al., 1998; Spoont, 1992). Stress from viewing unpleasant pictures might have increased endogenous 5-HT release, and SSRI might have potentiated 5-HT function to reduce reactivity of the amygdala in this study.

Interestingly, the effects of both SUL and FUL on the amygdala treatment were lateralized to the left side. It has been suggested regarding the functional laterality of the amygdala that the right amygdala may be first activated by emotional stimuli and be engaged in a rapid automatic processing of ambiguous information, while the left amygdala may be involved in a more specific sustained emotional reaction that decodes the arousal signaled by specific stimuli (Glascher and Adolphs, 2003). The reduced activity of the left amygdala might reflect reduction of the arousal. Since we used a rough self-rating score of unpleasantness, we did not have variations in terms of unpleasantness. If we had used a more detailed self-rating score of unpleasantness, the score might have detected the reduction of subjective unpleasantness. In addition, in terms of FLU treatment, it is perhaps worth remarking that, although the differences in mean signal changes elicited by unpleasant conditions compared to neutral condition in both left and right amygdala were similar, the right amygdala failed to reach a level of significance due to the greater variations in terms of the effect of SSRI treatment. Recent studies revealed that genetic variations of 5-HT transporters are associated with individual differences of right amygdala activity (Hariri et al., 2002b, 2005). Variations in the effect of SSRI treatment on the right amygdala could be attributable to genetic variations of 5-HT transporters.

Chronic successful treatments with SSRIs that normalized the elevated amygdala activity in patients with depression have been reported (Drevets, 2000). Since the therapeutic effect of SSRIs can take several weeks to appear, the mechanisms underlying the therapeutic effect of their chronic treatment are considered to be different from those of the acute pharmacological change induced by acute SSRI administration. However, our data suggest that even acute treatment of SSRIs could produce desirable preclinical

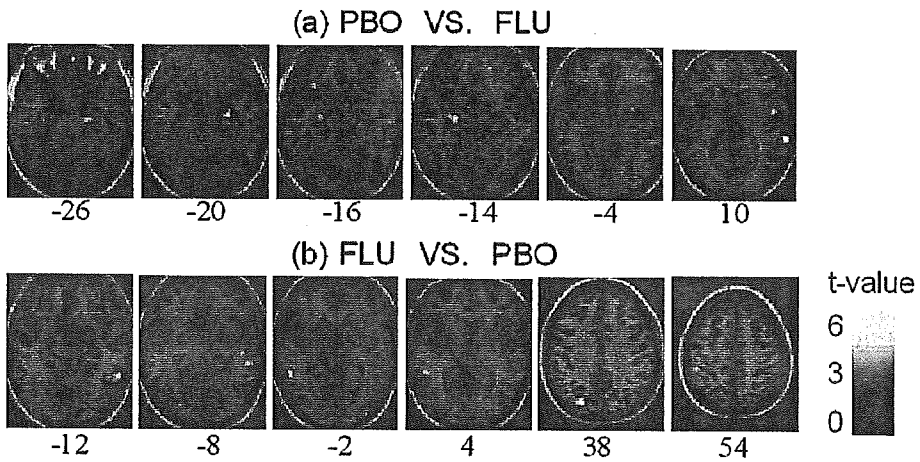

Fig. 3. Images showing manipulated brain activations in response to unpleasant condition relative to neutral condition under FLU treatment. Compared to PBO, attenuated activations were shown in the left OFC, right temporal cortex, right insula, right hippocampal region, left amygdaloid–hippocampal region, and right putamen (a). Enhanced activations were found in the temporal cortex and parietal cortex (b). Significant differences were recognized at a height threshold ($t > 3.05$; $P < 0.005$, uncorrected) and extent threshold (10 voxels). The bar shows the range of the t value. Within the image, L indicates left and R indicates right. Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

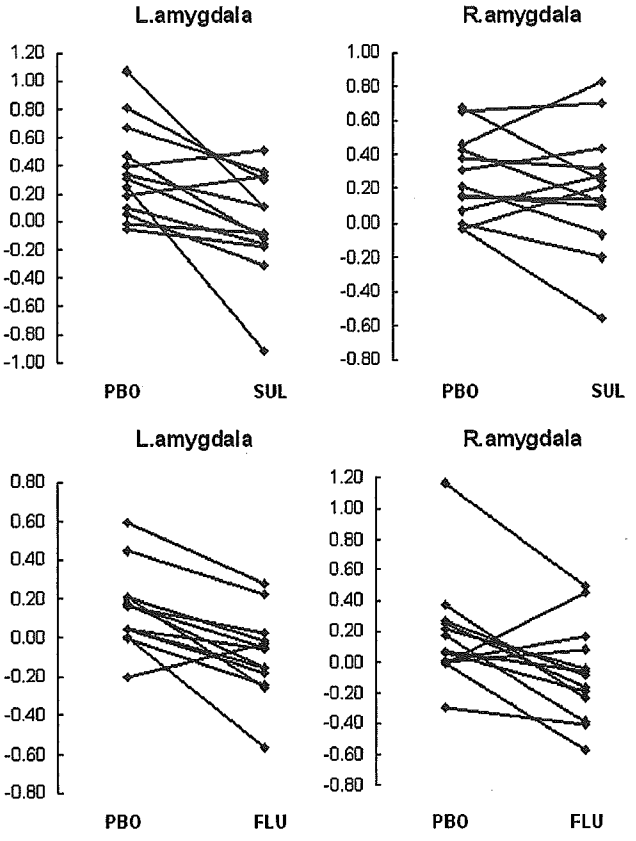

Fig. 4. Individual differences in the effect of drugs on amygdala activation elicited by unpleasant condition compared to neutral condition. The effect of sultopride on the left amygdala ($x, y, z = -14, -3, -22$) and the right amygdala ($x, y, z = 22, -3, -15$) (top). The effect of fluvoxamine on the left amygdala ($x, y, z = -24, -12, -11$) and the right amygdala ($x, y, z = 26, 1, -22$) (bottom). During both drugs treatments, mean signal changes elicited by unpleasant condition compared to neutral condition were significantly less than those during placebo treatment ($t = 2.63$, $P = 0.02$ and $t = 2.93$, $P = 0.01$, respectively) in the left amygdala, but not in the right amygdala ($t = 0.57$, $P = 0.57$ and $t = 1.93$, $P = 0.07$, respectively).

physiological changes, i.e., normalization of abnormally elevated amygdala activity, in patients with depression or anxiety disorders.

The present study has several limitations. First, it is possible that the drugs have effects not only on the specific neuronal activation but also on nonspecific vascular and respiratory systems that could, in turn, change BOLD signals. However, it could be considered that the observed regional BOLD changes mostly reflected the specific effects on neuronal responses because nonspecific effects would produce BOLD signal changes to a similar degree in any region across the brain (Honey and Bullmore, 2004). Moreover, we believed that nonspecific effects were minimized, if any, because the drugs induced minimal changes of physiological data. Second, we reported the drug effects on BOLD maps without correcting multiple comparisons. This raises the risk of type 1 errors. However, because pharmacological fMRI is a relatively new method and we do not possess sufficient information about the possible drug effects on BOLD signals across the whole brain, determining regions of interest (ROIs) a priori would be difficult. Therefore, we did not correct for multiple comparisons using ROIs.

Third, we examined the effects of DA D_2 receptor antagonists and SSRIs in healthy volunteers in this study. These drugs might not necessarily show similar actions in patients with psychiatric disorders, such as schizophrenia, mood disorders, and anxiety disorders. Studies on drug-free psychiatric disorder patients should be performed. Finally, despite significant changes of neural activation by pharmacological manipulation, behavioral results did not show significant changes. We had the subjects rate the pictures roughly using a 3-point scale. We aimed to simplify the emotional task and reduce cognitive demands during the scan since cognitive demands such as detailed evaluation or pressing several buttons could attenuate automatic emotional responses (Phan et al., 2002). Although this rough measurement might be attributable to insensitivity, conventional behavioral measurements are considered not sensitive enough to detect drugs effects (Honey and Bullmore, 2004).

In conclusion, we have shown that acute treatments of DA D_2 receptor antagonists and SSRIs commonly achieved considerable attenuation of amygdala activity, although the two treatments had different modulatory effects on other components of the neural circuit of emotional processing in healthy subjects.

The results suggest that the effects of the drug itself on BOLD signals are likely not negligible in fMRI studies aiming to investigate emotional processing in psychiatric patients taking drugs. At the same time, our findings suggest that pharmacological fMRI might be a powerful measurement tool for investigating the effects of drugs that manipulate neurotransmitter systems on emotional processing in the human brain and that this tool has potential for application in clinical practice and drug discovery.

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Symposium I

Intellectual Disability and Psychotic Disorders of Adult Epilepsy

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Summary: *Purpose:* To investigate the prevalence, psychopathology, and cognitive functions associated with psychotic disorders among adult epilepsy patients with intellectual disability (ID) based on a multicenter study in Japan.

Methods: The study was divided into three phases; a prevalence study of psychotic disorders among new referrals of epilepsy, a polydiagnostic comparative study of patients with psychotic epilepsy and those with schizophrenia, and a neuropsychological study of patients with psychotic epilepsy and education level–matched controls.

Results: Among 336 new referrals of epilepsy, a higher prevalence of psychotic disorders was found among patients with ID (24%) than among those with normal intelligence (6%). The psychotic symptoms and operational diagnoses of psychotic epilepsy patients with ID were similar to those of patients with normal intelligence. A wide range (7–86%) of psychotic epilepsy patients was diagnosed as having schizophrenia, depending on the operational criteria used. Patients with psychotic epilepsy had more disturbances in verbal memory and attention functions than did the controls.

Conclusions: Epilepsy patients with ID show a predisposition to develop psychotic disorders. Distinguishing their psychotic symptoms from those of schizophrenia is difficult. Subtle cognitive disturbances predispose to psychotic disorders in epilepsy. **Key Words:** Epilepsy—Intellectual disability—Psychotic disorder—Polydiagnosis—Symptomatology—Neuropsychology.

Many previous studies have reported that epilepsy patients with intellectual disability (ID) are liable to develop all types of psychiatric disorders, including psychotic disorders (1–4). Most clinicians believe that psychotic patients with ID lack the usual richness of the symptoms because of their inability to conceptualize their feelings and describe them to others, as well as an impoverished life experience. Psychotic symptoms are believed to be florid but banal, and to dominate delusions and hallucinations that reflect the naïve and wishful thinking, bizarre, impulsive, aggressive, and unpredictable behaviors. However, no evidence exists that the nature of the psychotic disorders in individuals with ID differs from those without (5). The prevalence, psychopathology, and association with cognitive dysfunction of psychiatric disorders among adult patients with epilepsy and ID require further clarification.

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SUBJECTS AND METHODS

We conducted a three-phase study on this issue. The first phase assessed the prevalence of psychotic disorders among new referrals of adult epilepsy by using a newly developed multiaxial classification scheme (6) based on a multicenter study in Japan (1). Next, we compared the symptoms and operational diagnoses between psychotic disorders in epilepsy and age- and sex-matched schizophrenia patients diagnosed with ICD-10 criteria by using the Japanese version of Operational Criteria Checklist for Psychotic Illness (J-OPCRIT) system (7). Finally, we compared the cognitive function among psychiatric disorders in epilepsy and age-, sex-, and education level–matched controls of epilepsy patients without psychiatric disorders and those with schizophrenia, by using a standardized neuropsychological test battery.

Exclusion criteria were the presence of severe ID with a lack of ability to communicate, alteration of consciousness during psychoses, personal history of alcohol abuse, and severe head trauma after the onset of epilepsy. Group differences were statistically analyzed by using χ^2 tests with Fisher's exact probability tests for nonparametric data and

TABLE 1. *Prevalence of psychotic disorders among new referrals with epilepsy*

	Epilepsy without ID	Epilepsy with ID	Group difference
Number of cases (male/female)	260 (130/130)	38 (21/17)	
Age (yr)	33.1 ± 12.2	27.8 ± 9.8	*a*
Age at onset of epilepsy (yr)	18.5 ± 12.9	12.1 ± 10.8	*b*
Type of epilepsy: PE/GE	74/25%	79/18%	*a*
Seizure frequency: free/yearly/monthly	8/48/44%	13/36/51%	*a*
Presence of epileptic discharges on EEG	66%	69%	NS
Presence of abnormal slow background EEG	38%	64%	*b*
Presence of history of brain damage	18%	59%	*b*
Presence of abnormal findings by CT/MRI	22%	48%	*b*
Presence of psychiatric disorders (ICD-10 category)	23%	66%	*b*
Organic mental disorders (F0)	1	5	*a*
Substance use disorders (F1)	1	0	NS
Psychotic disorders (F2)	6	24	*b*
Mood disorders (F3)	2	3	NS
Neurotic disorders (F4)	7	13	NS
Personality disorders (F6)	5	21	*b*

ID, Intellectual disability; PE/GE, partial epilepsy/generalized epilepsy; NS, not significant.
$^{a}p < 0.05$; $^{b}p < 0.01$ (χ^2 test/ ANOVA).

by using analysis of variance (ANOVA) and post hoc multiple comparisons by Fisher's PLSD for parametric data.

RESULTS

Prevalence of psychotic disorders among new referrals with epilepsy

Two hundred ninety-eight adult patients with epilepsy were included in the first phase of the study (Table 1). The organic feature was dominant among the epilepsy patients with ID compared with those without ID, reflected by higher frequencies of slow EEG activity, history of brain damage, and abnormal computed tomography (CT)/magnetic resonance imaging (MRI) findings. The prevalence of psychiatric and psychotic disorders was significantly higher in the epilepsy with ID group than in the without-ID group. The most prevalent psychiatric disorders were neurotic disorders (7%) in the without-ID group and psychotic disorders (24%) in the with-ID group. The second most prevalent disorders were psychotic disorders in the without-ID group (6%) and personality disorders (21%) in the with-ID group.

Clinical symptoms and operational diagnoses of epilepsy with a psychotic disorder and schizophrenia

Compared with the control group (56 patients with schizophrenia), the psychotic epilepsy groups (51 epilepsy patients without ID and 28 epilepsy patients with ID) were characterized by significantly lower frequencies of a family history of schizophrenia and deterioration of function from premorbid level, and higher ratios of abrupt onset of psychosis and remission (Table 2). The response rate of psychotic symptoms to neuroleptics was similar among all groups.

Psychotic symptoms were similar between the psychotic epilepsy groups without ID and with ID, characterized by a significantly higher frequency of accompanying affective symptoms and lower frequencies of negative and positive symptoms compared with those of the schizophrenia group. The operational diagnoses also were similar between the two psychotic epilepsy groups, and the schizophrenia diagnosis of them ranged from 7% to 68%, depending on the operational criteria used. Schneider's schizophrenia with first-rank symptoms was present to a similar degree in both of the psychotic epilepsy groups. Other prevalent diagnoses of the psychotic epilepsy were atypical psychosis by *Diagnostic and Statistical Manual of Mental Disorders–III* (DSM-III) or psychotic disorder not otherwise specified by DSM-IV.

Neuropsychological profiles of epilepsy with and without psychotic disorder and schizophrenia

Twenty-two psychotic epilepsy patients, 22 epilepsy patients without a psychiatric disorder, and 16 schizophrenia patients were enrolled in the neuropsychological study (Table 3). Wechsler Adult Intelligence Scale (WAIS)-R full-scale IQ, verbal IQ, and comprehension subscore were significantly lower in the psychotic epilepsy group than in the other two groups. Wechsler Memory Scale (WMS) memory quotient and nonrelated paired associate subscore, and WAIS-R digit symbol and picture-arrangement subscores were significantly lower in the psychotic epilepsy group than in the epilepsy group without a psychiatric disorder. WAIS-R similarity and digit span subscores were significantly lower in the psychotic epilepsy group than in the schizophrenia group. WAIS-R performance IQ and WCST category number did not differ among the three groups.

TABLE 2. *Symptoms and operational diagnoses of schizophrenia and epilepsy with a psychotic disorder*

Group	Schizophrenia	Epilepsy without ID	Epilepsywith ID	Group difference
Number of cases (male/female)	56 (26/30)	51 (24/27)	28 (18/10)	
Age (yr)	38.5 ± 11.8	35.0 ± 11.4	38.1 ± 16.6	NS
Age at onset of epilepsy (yr)	–	13.1 ± 7.8	12.3 ± 13.4	NS
Age at onset of psychosis (yr)	25.0 ± 9.9	28.0 ± 10.1	29.6 ± 12.6	NS
Family history of schizophrenia	27%	4%	7%	*a*
Mode of onset: abrupt/acute/gradual	16/23/60%	40/27/40%	43/25/36%	*b*
Course: remission/recurrent/chronic	18/36/47%	54/10/35%	50/14/36%a	*a*
Deterioration from premorbid function	66%	22%	21%	*a*
Response to neuroleptics	73%	75%	57%	NS
Clinical symptoms				
Lack of insight	88%	65%	71%	*b*
Delusions/hallucinations last for 1 wk	73	43	61	*a*
Loss of energy	68	29	11	*a*
Blunted affect	57	18	11	*a*
Slowed activity	55	25	18	*a*
Restricted affect	55	20	14	*a*
Primary delusional perception	50	10	18	*a*
Bizarre behavior	48	65	64	*b*
Abusive/accusatory/persecutory voices	43	14	14	*a*
Well-organized delusions	38	6	11	*a*
Negative formal thought disorder	36	16	7	*a*
Third-person auditory hallucinations	36	8	0	*a*
Delusions of passivity	23	8	4	*b*
Positive formal thought disorder	16	6	0	*b*
Accompanying affective symptoms	14	41	25	*b*
Diminished libido	13	2	0	*b*
Operational diagnosis of schizophrenia				
ICD-10 schizophrenia	100%	49%	50%	*a*
Taylor & Abrahams' schizophrenia	96	49	57	*a*
RDC schizophrenia	85	43	68	*a*
Carpenter's schizophrenia	72	68	50	NS
Schneider's schizophrenia	71	37	39	*a*
DSM-III-R schizophrenia	70	27	25	*a*
DSM-IV schizophrenia	63	18	21	*a*
DSM-III schizophrenia	63	16	14	*a*
French chronic schizophrenia	57	14	7	*a*
St. Louis' schizophrenia	55	18	7	*a*

ID, Intellectual disability; NS, not significant.
$^a p < 0.01$; $^b p < 0.05$ (χ^2 test/analysis of variance).

DISCUSSION

The present study confirmed that the presence of ID, which may stem from organic brain dysfunction, in epilepsy patients is a risk factor for developing a psychotic disorder. However, psychotic symptoms and psychiatric diagnoses were similar in epilepsy patients with ID and those without ID. Among the general population with ID, the similarities in psychopathology between patients with normal intelligence and those with mild ID have already been documented (8). Although patients with psychotic epilepsy showed lower frequencies of negative and positive symptoms than did schizophrenic patients, a significant number of them were diagnosed as having schizophrenia. The presence of nuclear schizophrenia symptoms are in line with previous reports on psychotic epilepsy patients without ID (9–11) as well as those with ID (12). Although some previous reports pointed out that a low IQ is a risk factor for a chronic course of psychoses in epilepsy (13,14), the present results suggest that the prognosis of epileptic psychosis is better than that of schizophrenia. The discrepancy may be due to the exclusion of severe ID patients in the present study.

The attention and verbal factors revealed by WAIS-R (15), as well as verbal memory detected by WMS, were poorer in the psychotic epilepsy patients than in the controls. These results support the hypothesis that psychotic disorders in epilepsy are associated with underlying cognitive defects (11,14,16). Mellers et al. (17) reported that epilepsy patients with schizophrenia-like psychosis showed a global cognitive dysfunction comparable to that of schizophrenia. Caplan et al. (18) hypothesized that illogical thinking stemming from global cognitive dysfunction in epilepsy contributes to the development of schizophrenia-like psychosis. Verbal dysfunction and attentional deficits, which may result in a reduced capacity to deal with complex social problems, may predispose to psychotic disorders in epilepsy.