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Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study

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Abstract

Human lesion or neuroimaging studies suggest that amygdala is involved in facial emotion recognition. Although impairments in recognition of facial and/or emotional expression have been reported in schizophrenia, there are few neuroimaging studies that have examined differential brain activation during facial recognition between patients with schizophrenia and normal controls. To investigate amygdala responses during facial recognition in schizophrenia, we conducted a functional magnetic resonance imaging (fMRI) study with 12 right-handed medicated patients with schizophrenia and 12 age- and sex-matched healthy controls. The experiment task was a type of emotional intensity judgment task. During the task period, subjects were asked to view happy (or angry/disgusting/sad) and neutral faces simultaneously presented every 3 s and to judge which face was more emotional (positive or negative face discrimination). Imaging data were investigated in voxel-by-voxel basis for single-group analysis and for between-group analysis according to the random effect model using Statistical Parametric Mapping (SPM). No significant difference in task accuracy was found between the schizophrenic and control groups. Positive face discrimination activated the bilateral amygdalae of both controls and schizophrenics, with more prominent activation of the right amygdala shown in the schizophrenic group. Negative face discrimination activated the bilateral amygdalae in the schizophrenic group whereas the right amygdala alone in the control group, although no significant group difference was found. Exaggerated amygdala activation during emotional intensity judgment found in the schizophrenic patients may reflect impaired gating of sensory input containing emotion.

Keywords: Face; Emotion; Amygdala; fMRI; SPM; Schizophrenia

1. Introduction

Patients with schizophrenia often perform poorly in social situations. Previous studies reported that they had been less accurate than normal controls in facial

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identity matching requiring whether pairs of faces were the same or different persons (Feinberg et al., 1986) and the patients with paranoia had experienced other people as directing attention toward them when in reality attention was not being directed at them (Rosse et al., 1994; Franck et al., 1998). Moreover, they have performed worse than normal controls in recognition of facial expression of emotion (Walker et al., 1984; Feinberg et al., 1986; Heinmberg et al., 1992); for example, in emotion matching to decide the same or different emotions in pairs of faces or emotion labeling to decide linguistic labels of emotional faces. These impairments in recognizing facial and/or emotional expression may be related to the misinterpretation of social interactions or to the flat effect commonly found in schizophrenia.

The patients with bilateral amygdalotomy or bilateral amygdala damage were poor in the recognition of facial identity or facial emotion, especially fearful face (Adolphs et al., 1994, 1999; Anderson and Phelps, 1998). Recent neuroimaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) reported that the amygdala was activated during emotional face perception (Schneider et al., 1995; Morris et al., 1998; Paradiso et al., 1999; Blair et al., 1999). It is strongly conceivable, therefore, that the amygdala is related to recognition of faces and emotions (LeDoux, 2000; Davis and Whalen, 2001).

Amygdala abnormalities in schizophrenia have been reported in postmortem and neuroimaging studies (Bogerts et al., 1985; Breier et al., 1992; Pearlson et al., 1997), in which schizophrenics showed reduced amygdala volume compared with controls.

To date, only two activation studies in emotional face recognition have been published in schizophrenia. An fMRI study reported that schizophrenic patients did not demonstrate amygdala activation during sad mood induction looking at sad facial expressions, despite significant amygdala activation in normal controls (Schneider et al., 1998). Another fMRI study also found that schizophrenics showed no amygdala activation during gender discrimination of faces depicting fearful faces, despite left amygdala activation in normal controls (Phillips et al., 1999). In the same study, non-paranoid schizophrenic patients categorized a disgusted face as an angry or fearful face in the identification task and it was demonstrated in the response to disgusted expressions activation in the amygdala, a region associated with perception of fearful faces.

The present study investigated the difference in amygdala response during facial recognition between patients with schizophrenia and normal controls using fMRI. The task used in the present study was a type of emotional intensity judgment task, while in the two previous activation studies of schizophrenia one used a mood induction task and the other an implicit task with regard to emotional face processing. In the emotional intensity judgment task, subjects were required to judge and interpret emotional faces, although the mood induction and gender discrimination task did not require such cognitive processes. Imaging data were analyzed in a voxel-by-voxel basis for single-group analysis and for between-group analysis according to the random effect model using Statistical Parameter Mapping (SPM) 99. Since the region focused in the present study was the bilateral amygdalae, the correction for the multiple comparisons was restricted to those structures.

We hypothesized that schizophrenic patients would show different amygdala activation compared with normal controls during recognition of faces with positive or negative emotion. The present findings showed that the patients demonstrated more prominent activation than the controls in the right amygdala during positive face discrimination.

2. Methods

2.1. Subjects

The patient group consisted of 12 patients with a DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia (six men and six women; aged 18 to 33 years, mean 26.0 years, SD = 4.5; mean duration of illness 3.8 years, SD = 3.5). They were outpatients or inpatients from the Department of Neuropsychiatry of Fukui Medical University. Ten patients were on neuroleptic medication (mean chlorpromazine equivalent daily dose 322.0 mg, SD = 264.1) and two patients were unmedicated at the time of fMRI examination. Mean symptom scores were 31.9, SD = 8.1 on the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962), and 56.3, SD = 14.4 (positive, 11.3, SD = 4.6; negative, 16.3, SD = 4.5; general, 28.8,

SD = 7.3) on the Positive and Negative Syndromes Scale (PANSS, Kay, 1991). Twelve healthy volunteers (six men and six women; aged 22 to 30 years, mean 24.4 years, SD = 2.4) were recruited as controls, without a history of neurological, psychiatric disease, and drug or alcohol abuse. None were taking medication that could affect the cerebral blood flow.

Before the experiment a shorter version of the experimental task was administered to confirm that subjects could perform at an average level. As assessed by a series of *t*-tests, the schizophrenic and control groups did not differ in age or depressive affect as measured by the Zung Self-rating Depression Scale (Zung-SDS, Zung, 1965: patients, 42.8, SD = 9.1; controls, 35.9, SD = 8.1), but they did differ in the years of education ($p < 0.05$: patients, 13.5 years, SD = 2.3; controls, 16.5, SD = 0.8). All subjects were strongly right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The protocol was approved by the Ethical Committee of Fukui Medical University, and all subjects gave written informed consent for the study.

2.2. Experimental design

Digitized grayscale pictures of 24 unfamiliar faces (12 male and 12 female) with negative (angry, disgusting or sad), positive (happy), and neutral emotion were used as materials. To establish the validity and reliability of the facial stimuli used, a sample of 10 healthy controls was asked to rate each face according to emotion type and intensity. The subjects were required to label each face as one of negative or positive emotion and rate the emotional intensity on a verbal analog scale ranging from −5 to 5 (−5 = extremely negative, 0 = neutral, 5 = extremely positive). The probability that the emotional face was correctly labeled was 98% and 99% for the negative and positive faces, respectively. Average rating score of the emotional intensity was -2.6 ± 0.3 for the negative, 2.5 ± 0.4 for the positive, and 0.1 ± 0.1 for the neutral face. An analysis of variance (ANOVA) revealed a significant effect of emotional intensity ($p < 0.01$), and post hoc Scheffe's test demonstrated significant differences between the ratings of the neutral and positive faces,

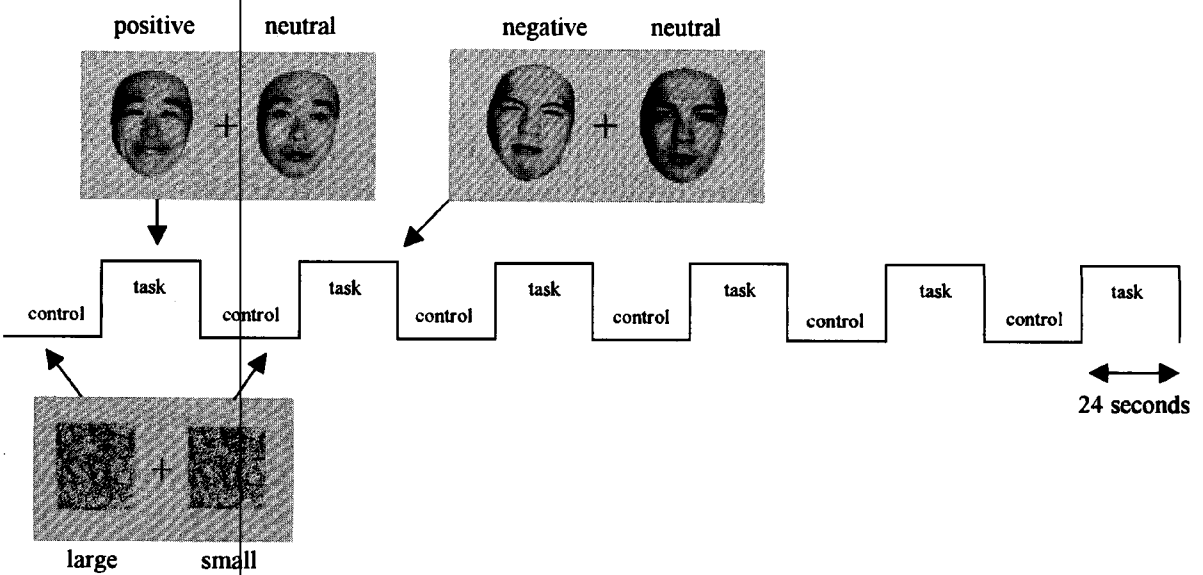

Fig. 1. The experiment consisted of two face conditions (positive and negative face discrimination) and a control condition. In each block of the face discrimination, a face with positive (happy) or negative (angry, disgusting or sad) emotion was paired with the same face with a neutral emotion. The subjects judged which face was emotional. In the control condition, the subjects were instructed to discriminate the size of two rectangles and indicate which one was larger. The experiment was composed of 12 blocks (six control blocks, three positive and three negative face discrimination blocks) and the order of the two face discriminations was counterbalanced across subjects.

the neutral and negative faces, and the positive and negative faces ($p<0.01$, respectively).

The experiment consisted of 12 blocks, six blocks each of control and task conditions; each block was 24 s long, alternating control and task. The task condition contained two kinds of face discrimination, i.e., three positive and three negative face discriminations (Fig. 1). The order of the positive or negative face discriminations was counterbalanced across subjects. During the positive face discrimination, happy and neutral faces were simultaneously presented at a rate of 2.8 s/pairs with a 0.2-s inter-stimulus interval. During the negative face discrimination, an angry, disgusting, or sad face and neutral face were presented. A list of eight face-pairs was assigned to each block and the side of the emotional and neutral face was randomized within the list. The subjects were instructed to judge which face was more emotional and to indicate by elevating the index (left side) or middle (right side) finger of their right hands. During the control condition, the subjects were instructed to compare the size of two rectangles placed side-by-side and to indicate which one was larger by elevating their right index or middle finger. Those stimuli were presented at the same rate and in the same format as the stimuli in the task condition. During scanning, the stimuli were projected onto a half transparent screen using an LCD projector connected to a personal computer in which the stimuli were generated. The subjects saw the stimuli through a tilted mirror attached to the head coil of the scanner. The subjects' responses were inspected and recorded visually.

2.3. Image acquisition and analysis

A time course series of 100 volumes was acquired using T2*-weighted, gradient echo, EPI sequences with a 1.5 T MR imager (Signa Horizon; General Electric Medical Systems, Milwaukee, WI, USA) and a standard birdcage head coil. Each volume consisted of 12 coronal slices, with a slice thickness of 4 mm, with a 1-mm gap, to cover the amygdala. The time interval between two successive acquisitions of the same image was 3000 ms, echo time was 40 ms, and flip angle was 90°. The digital in-plane resolution was 64 × 64 pixels with a pixel dimension of 3.75 × 3.75 mm. The anatomical image was also acquired (2D-FSE: TR = 3 s, TE = 80 ms, Flip Angle = 90°, 256 × 256 matrix and 34–36 coronal slices of 4 mm thickness with a 1-mm gap). Tight but comfortable foam padding was placed around the subject's head to minimize head motion. After discarding the first four images due to the unsteady longitudinal magnetization, the successive 96 EPI images (eight images per block) were subjected to analysis. Image processing and statistical analysis was performed using SPM99 (the Wellcome Department of Cognitive Neurology, London, UK). Firstly, to correct for dislocations caused by head motion, all EPI images were realigned. Then,

Table 1
Significant BOLD signal changes in amygdala during face discrimination compared with control condition

	Positive face discrimination					Negative face discrimination				
	x	*y*	*z*	Z-value	*P*-value	*x*	*y*	*z*	Z-value	*P*-value
Single-group analysis										
Controls										
L amygdala	−22	−6	−8	3.72	0.016					n.s.
R amygdala	20	0	−16	3.79	<0.001	22	−2	−10	3.22	0.016
Schizophrenics										
L amygdala	−18	−4	−10	3.15	0.020	−20	−6	−14	3.97	0.001
R amygdala	20	−6	−10	5.20	<0.001	20	−2	−12	4.99	<0.001
Between-group analysis										
Controls > Schizophrenics										
					n.s.					n.s.
Schizophrenics > Controls										
R amygdala	22	−6	−12	3.49	0.010					n.s.

L, Left; R, Right; *x*, *y*, *z*, stereotaxic coordinates as given in the Talairach and Tournoux atlas. The probability threshold was $p<0.025$ after correction for multiple comparison (the search region was restricted to the bilateral amygdalae).

these images were normalized to the Montreal neurological institute (MNI) atlas (Evans et al., 1994) using the parameter obtained from the normalization process of the anatomical image that was coregistered to the first EPI image beforehand. Finally, the images were smoothed using an 8-mm Gaussian kernel.

2.4. Statistical analysis

Firstly, analysis was performed on an individual basis. The mean signal intensity of the imaged brain areas was proportionally scaled to 100 arbitrary units for each functional image volume in order to remove the effect of global signal change. The expected signal changes caused by the tasks were modeled with a box-car function convolved with hemodynamic response function and regression analysis was performed for each and every voxel. Signal drifts below 1/96 Hz were also modeled and excluded form the analysis to avoid artifacts. The analysis made two contrast images that held percent signal change values at each voxel for the positive and negative face discrimination tasks compared with the control. To make inferences at a single-group level (Friston et al., 1999), these images were analyzed with one-sample *t*-tests on a voxel-by-voxel basis. In the between-group analysis, contrast images were entered into a two-sample *t*-test. To avoid confounding effects of relative deactivation in one group, the analysis was masked with activation during two face discrimination tasks in all 24 subjects ($p=0.05$). The resulting areas of activation were characterized in terms of their peak. The statistical threshold was at $p<0.001$ ($T=3.50$) for each voxel. Since our hypothesis existed only in bilateral amygdala (8.0 mm spheres at Talairach coordinates (Talairach and Tournoux, 1988) of [−22, −6, −16] and [22, −6, −16]), small volume correction for multiple comparisons were conducted at extent threshold of $p<0.025$ for each of the two regions.

3. Results

3.1. Task performance

The mean (± SD) percentage of correct responses between the two groups showed no significant difference for the positive face discrimination (normal subjects, 97.2 ± 4.8%; schizophrenic subjects, 95.1 ± 5.3%) and for the negative face discrimination (92.0 ± 7.8% and 95.8 ± 5.3%, respectively). Two-way repeated-measure ANOVAs showed no significant main effect of group ($F=0.29$, $df=1, 22$, $p=0.59$) or condition ($F=1.56$, $df=1, 22$, $p=0.23$), or interaction ($F=2.65$, $df=1, 22$, $p=0.12$). Both groups performed at the ceiling level during the control condition (over 99% correct).

3.2. Neuroimaging data

During the positive face discrimination compared with the control condition, both the control and schizophrenic groups showed significant activation in the bilateral amygdalae (controls; left amygdala

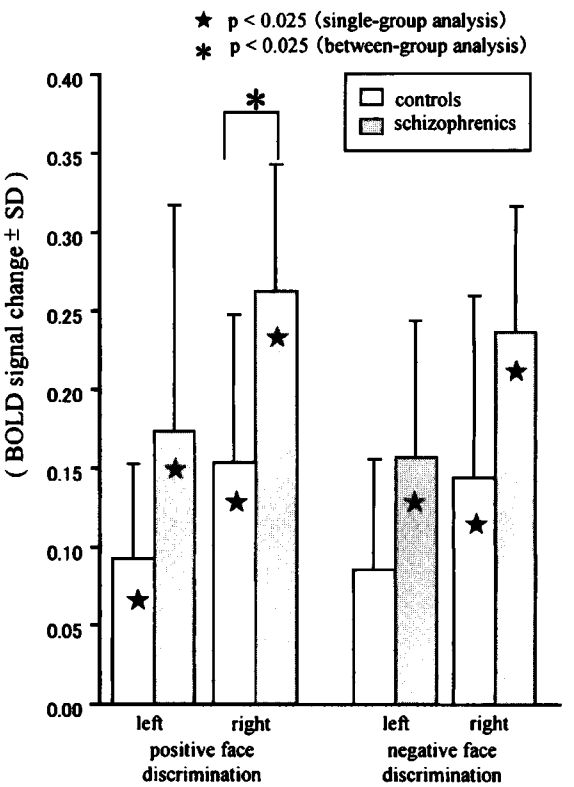

Fig. 2. Graphical representation of BOLD signal changes in the bilateral amygdalae across the control group and the schizophrenic group during positive and negative face discrimination compared with control condition. Bars represent standard deviations. Stars show significant activation for single-group analysis and asterisk shows significant activation for between-group analysis.

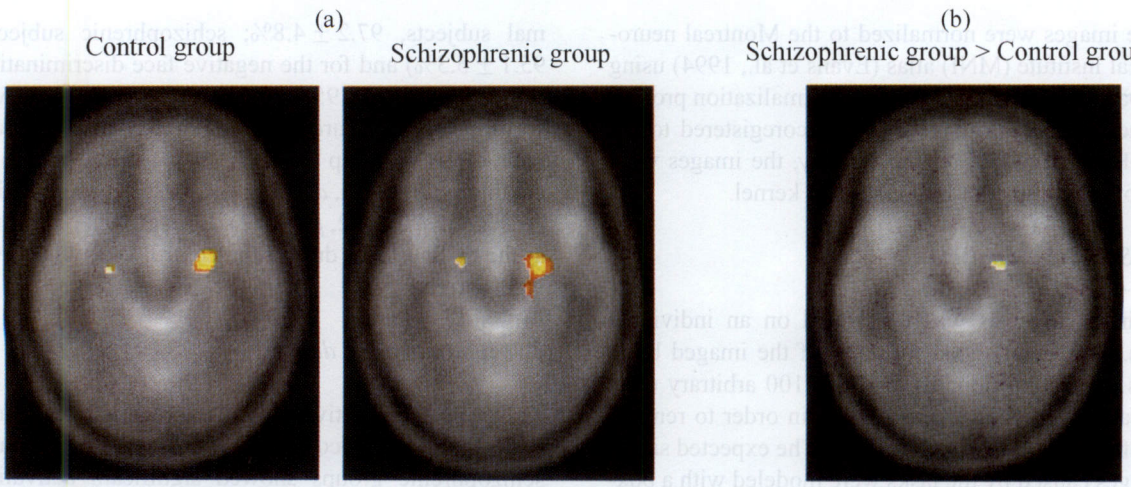

Fig. 3. (a) Significant bilateral amygdalae activation during the positive face discrimination for the control (left) and schizophrenic (right) groups superimposed on the MNI normalization template images. Since the search region was restricted to the bilateral amygdalae (8.0 mm sphere at [−22, −6, −16] and [22, −6, −16]), small volume correction for multiple comprisons were conducted at extent threshold of $p<0.025$ for each of the two regions. (b) The results for group comparison during the positive face discrimination. The schizophrenic group showed greater activation in the right amygdala compared with the control group (correction for multiple comparison, $p=0.010$).

$p=0.016$, right amygdala $p<0.001$: schizophrenics; left $p=0.020$, right $p<0.001$). The schizophrenic group showed more prominent activation than the control group in the right amygdala during the positive face discrimination ($p=0.010$) (Table 1, Fig. 2).

During the negative face discrimination compared with the control condition, the control group showed significant activation in the right amygdala ($p=0.016$), while the schizophrenic group showed significant activation in the bilateral amygdalae (left $p=0.001$; right $p<0.001$). However, there was no significant difference between groups during the negative face discrimination (Table 1, Fig. 2).

Fig. 3a shows significant activation of the bilateral amygdalae during the positive face discrimination in the control and schizophrenic groups, and Fig. 3b shows greater activation of the right amygdala in the schizophrenic group than in the control group.

In the schizophrenic group, there was no significant correlation between the task-related signal change of the amygdala and daily neuroleptic dosage during both face discrimination tasks (a Pearson's correlation analysis, $p>0.05$).

To determine whether the patient and control groups exhibited differences in amygdala activation due to laterality and task condition, we conducted three-way ANOVA for the percentage signal changes in the amygdala; factors were Group (patients, controls), Laterality (left, right), and Task condition (positive, negative face discrimination). While the ANOVA revealed significant main effects of Group ($F=20.74$, $df=1, 22$, $p<0.001$) and Laterality ($F=13.83$, $df=1, 22$, $p<0.001$), no significant main effect of Task condition ($F=0.599$, $df=1, 22$, $p=0.441$) and interactions between Group × Laterality ($F=0.449$, $df=1, 22$, $p=0.504$), Group × Task condition ($F=0.109$, $df=1, 22$, $p=0.743$), Laterality × Task condition ($F=0.026$, $df=1, 22$, $p=0.872$), and Group × Later-Laterality × Task condition ($F=0.009$, $df=1, 22$, $p=0.927$) were observed.

4. Discussion

We hypothesized that schizophrenic patients would show different amygdala activations during facial recognition compared with normal controls. In fact, the present patient group showed greater amygdala activation than the control group.

Most of the present schizophrenic patients were taking neuroleptics at the fMRI examination. The effects of those medications on signal intensity changes are not yet understood, and some studies during motor task performance have suggested that

neuroleptics influence fMRI activation patterns of schizophrenic patients (Wenz et al., 1994; Braus et al., 1999). With respect to the effects on amygdala activation, Schneider et al. (1998) found no correlation between signal intensity in the amygdala and the dose of neuroleptics. In addition, Phillips et al. (1999) indicated that more abnormal responses were demonstrated by non-paranoid schizophrenics, who were on a lower dose of medication, compared with paranoid patients. In the present study, there was also no significant correlation between medication and amygdala activation during each task condition, suggesting little influence of neuroleptics on the present findings.

Two previous fMRI studies of emotional processing in schizophrenia reported that patients with schizophrenia showed less amygdala activation than normal controls (Schneider et al., 1998; Phillips et al., 1999). However, the present study demonstrated contrasting findings of differential amygdala activation, i.e., greater amygdala activation in the schizophrenics compared with the controls. One possible explanation for these inconsistent findings is the differences in the experimental paradigms. One of the previous studies used a mood induction task in which subjects look at happy or sad facial expressions and use them to help feeling happy or sad, and another used an implicit task with regard to emotional processing in which subjects were required to discriminate the gender of faces depicting fearful expressions. However, the task used in the present study was a type of explicit task. The present explicit task required judgment and interpretation of emotional faces, although a mood induction and gender discrimination task causes a greater instinctive emotional reaction without such cognitive processes. A previous fMRI study in normal volunteers (Hariri et al., 2000) showed that decreased amygdala activation correlated with increased activity in the right inferior frontal gyrus during an emotion labeling task, in which subjects were required to judge and interpret emotional expressions similar to the present explicit task. Thus, the functional network between the amygdala and prefrontal cortex may have some influence on the brain activation during the performance of the task used in the present study.

However, since the present study was designed to obtain sufficient resolution to detect the activation of a small structure, the amygdala, using a 1.5 T MR scanner, our slice selection did not allow for whole brain coverage. Future studies using a high-field Tesla MR scanner to cover the whole brain are needed to clarify whether the functional network between the amygdala and other regions (e.g., prefrontal cortex) is impaired in schizophrenia.

The between-group analysis showed a significant difference only in the right amygdala activation during the positive face discrimination. The right hemisphere is often considered to contribute to emotion-related information processing (Morrison et al., 1988; Adolphs et al., 2000). It has been suggested that the right hemisphere hypersensitivity to emotional material is the functional basis of schizophrenia (Oepen et al., 1987). Therefore, the right amygdala overactivation observed in the present study might help explain the negative (i.e., paranoid) attributions made to human or other environmental stimuli in patients with schizophrenia. However, the amygdala responses showed no significant interactions between Group × Laterality, Group × Task condition, and Group × Laterality × Task condition. Thus, the schizophrenic group had a tendency toward greater amygdala activation bilaterally during both task conditions (Fig. 2). In the present study, we could not conclude on the laterality of the amygdala activation or the difference of amygdala responses to the different types of emotion (positive or negative emotion) in schizophrenia.

Several studies reported thalamic abnormalities in schizophrenic patients (Pakkenberg, 1990; Braff, 1993; Andreasen et al., 1994; Buchsbaum et al., 1996). Since the thalamus receives input from the cortical, subcortical, and brainstem nuclei and plays an important role in filtering stimuli and sensory gating, it has been suggested that patients with schizophrenia may be flooded with information and experience the signs and symptoms of schizophrenia such as delusions, hallucinations, or negative symptoms (Andreasen et al., 1994).

Limbic structures are also hypothesized to contribute to symptom formation in schizophrenia. Using PET, Liddle et al. (2000) showed significant decreases in metabolism in the ventral striatum, thalamus and frontal cortex of the first-episode schizophrenics after the first dose of antipsychotic treatment, and a significant relationship between the reduction in metabolism in the left hippocampus after the first dose treatment and the subsequent reduction in reality distortion after

6 weeks of treatment. Together with the evidence that the hippocampus gates the cortico-striato-thalamo-cortical feedback loops, these findings have been interpreted as indicating that aberrant hippocampal firing is involved in the generation of delusions and hallucinations, and overactivity in the cortico-striato-thalamic circuits is associated with acute psychosis, irrespective of symptom profile.

The amygdala is also one of the major sensory stations and receives an enormous array of convergent sensory information from the unimodal sensory cortex (visual, auditory and somatosensory), and polysensory and limbic association areas (Aggleton, 1993). Since neuroimaging and lesion studies suggested that the amygdala was implicated in the interpretation of emotional significance of sensory stimuli such as facial expressions, it is suggested that the amygdala may play a significant role in filtering, gating, and processing emotional information. Exaggerated amygdala activation during emotional intensity judgment observed in our schizophrenic patients may suggest that an impaired sensory gating in this structure results in flooding with information that contains emotional significance. Consequently, schizophrenics may have a predisposition to display an inappropriate mood, a loss of control over emotion, or affective flattening, or have difficulty identifying other people's emotional status.

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References

Adolphs, R., Tranel, D., Damasio, H., Damasio, A., 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372, 669–672.

Adolphs, R., Tranel, D., Hamann, S., Young, A.W., Calder, A.J., Phelps, E.A., Anderson, A., Lee, G.P., Damasio, A.R., 1999. Recognition of facial emotion in nine individuals with bilateral amygdala damage. Neuropsychologia 37, 1111–1117.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., Damasio, A.R., 2000. A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. J. Neurosci. 20, 2683–2690.

Aggleton, J.P., 1993. The contribution of the amygdala to normal and abnormal emotional states. Trends Neurosci. 16, 328–333.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. APA, Washington, DC.

Anderson, A.K., Phelps, E.A., 1998. Intact recognition of vocal expression of fear following bilateral lesions of the human amygdala. NeuroReport 9, 3607–3613.

Andreasen, N.C., Arndt, S., Swayze, V., Cizadlo, T., Flaum, M., O'Leary, D., Ehrhardt, J.C., Yuh, W.T., 1994. Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. Science 266, 294–298.

Blair, R.J.R., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122, 883–893.

Bogerts, B., Meertz, E., Schonfeldt-Bausch, R., 1985. Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. Arch. Gen. Psychiatry 42, 784–791.

Braff, D.L., 1993. Information processing and attention dysfunctions in schizophrenia. Schizophr. Bull. 19, 233–259.

Braus, D.F., Ende, G., Weber-Fahr, W., Sartorius, A., Krier, A., Hubrich-Ungureanu, P., Ruf, M., Stuck, S., Henn, F.A., 1999. Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. Schizophr. Res. 39, 19–29.

Breier, A., Buchanan, R.W., Elkashef, A., Munson, R.C., Kirkpatrick, B., Gellad, F., 1992. Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch. Gen. Psychiatry 49, 921–926.

Buchsbaum, M.S., Someya, T., Teng, C.Y., Abel, L., Chin, S., Najafi, A., Haier, R.J., Wu, J., Bunney Jr., W.E., 1996. PET and MRI of the thalamus in never-medicated patients with schizophrenia. Am. J. Psychiatry 153, 191–199.

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Mol. Psychiatr. 6, 13–34.

Evans, A.C., Kamber, M., Collins, D.L., Macdonald, D., 1994. An MRI-based probablistic atlas of neuroanatomy. In: Shorvon, S., Fish, D., Andermann, F., Bydder, G.M., Stefan, H. (Eds.), Magnetic Resonance Scanning and Epilepsy. NATO ASI series A: Life Sciences, Plenum, New York, vol. 264, pp. 263–274.

Feinberg, T.E., Rifkin, A., Schaffer, C., Walker, E., 1986. Facial discrimination and emotional recognition in schizophrenia and affective disorders. Arch. Gen. Psychiatry 43, 276–279.

Franck, N., Daprati, E., Michel, F., Saoud, M., Dalery, J., Marie-Cardine, M., Georgieff, N., 1998. Gaze discrimination is unimpaired in schizophrenia. Psychiatry Res. 81, 67–75.

Friston, K.J., Holmes, A.P., Worsley, K.J., 1999. How many subjects constitute a study? Neuroimage 10, 1–5.

Hariri, A.R., Bookheimer, S.Y., Mazziotta, J.C., 2000. Modulating emotional response: effects of a neocortical network on the limbic system. NeuroReport 11, 43–48.

Heinmberg, C., Gur, R.E., Erwin, R.J., Shtasel, D.L., Gur, R.C., 1992. Facial emotion discrimination: III. Behavioral findings in schizophrenia. Psychiatry Res. 42, 253–265.

Kay, S.R., 1991. Positive and Negative Syndromes in Schizophrenia. Brunner/Mazel, New York.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184.

Liddle, P.F., Lane, C.J., Ngan, E.T., 2000. Immediate effects of risperidone on cortico-striato-thalamic loops and the hippocampus. Br. J. Psychiatry 177, 402–407.

Morris, J.S., Friston, K.J., Büchel, C., Frith, C.D., Young, A.W., Calder, A.J., Dolan, R.J., 1998. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 121, 47–57.

Morrison, R.L., Bellack, A.S., Mueser, K.T., 1988. Deficits in facial-affect recognition and schizophrenia. Schizophr. Res. 14, 67–83.

Oepen, G., Fünfgeld, M., Höll, T., Zimmermann, P., Landis, T., Regard, M., 1987. Schizophrenia—an emotional hypersensitivity of the right cerebral hemisphere. Int. J. Psychophysiol. 5, 261–264.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.

Pakkenberg, B., 1990. Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. Arch. Gen. Psychiatry 47, 1023–1028.

Paradiso, S., Johnson, D.L., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 1999. Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. Am. J. Psychiatry 156, 1618–1629.

Pearlson, G.D., Barta, P.E., Powers, R.E., Menon, R.R., Richards, E.H., Aylward, E.H., Federman, E.B., Chase, G.A., Petty, R.G., Tien, A.Y., 1997. Ziskined–Somerfeld Research Award 1996. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol. Psychiatry 41, 1–14.

Phillips, M.L., Williams, L., Senior, C., Bullmore, E.T., Brammer, M.J., Andrew, C., Williams, S.C.R., David, A.S., 1999. A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. Psychiatry Res. 92, 11–31.

Rosse, R.B., Kendrick, K., Wyatt, R.J., Isaac, A., Deutsch, S.I., 1994. Gaze discrimination in patients with schizophrenia: preliminary report. Am. J. Psychiatry 151, 919–921.

Schneider, F., Gur, R.E., Mozely, L.H., Smith, R.J., Mozely, P.D., Censits, D.M., Alavi, A., Gur, R.C., 1995. Mood effects on limbic blood flow correlate with emotional self-rating: a PET study with oxygen-15 labeled water. Psychiatry Res. 61, 265–283.

Schneider, F., Weiss, U., Kessler, C., Salloum, J.B., Posse, S., Grodd, W., Müller-Gärtner, H.W., 1998. Differential amygdala activation in schizophrenia during sadness. Schizophr. Res. 34, 133–142.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Walker, E., McGuire, M., Bettes, B., 1984. Recognition and identification of facial stimuli by schizophrenics and patients with affective disorders. Br. J. Clin. Psychol. 23, 37–44.

Wenz, F., Schad, L.R., Knopp, M.V., Baudendistel, K.T., Flomer, F., Schroder, J., van Kaick, G., 1994. Functional magnetic resonance imaging at 1.5 T: activation pattern in schizophrenic patients receiving neuroleptic medication. Magn. Reson. Imaging 12, 975–982.

Zung, W.W.K., 1965. A self-rating depression scale. Arch. Gen. Psychiatry 12, 63–70.